SLEEP AND CARDIOMETABOLIC HEALTH IN ADULTS: CONTRIBUTIONS OF LIFESTYLE AND DIETARY FACTORS, OBJECTIVE VS. SUBJECTIVE SLEEP, AND CHANGE IN SLEEP HABITS

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Abstract

Sleep is necessary for cardiometabolic health, but compared to the 1980s, greater proportions of adults in developed countries are sleep deprived. The primary objectives of this dissertation were three-fold: i) to estimate the contributions of inflammation, oxidative stress, antioxidants, and physical activity levels to the causal relationships between sleep and cardiometabolic health; ii) to correlate objective vs. subjective measures of sleep, and determine if the correlations vary in subpopulations; and, iii) to estimate the risk of developing hypertension, diabetes, dyslipidemia and obesity due to changes in objectively measured sleep duration and efficiency in a 4 y follow-up. The US National Health and Nutritional Examination Survey and the Sleep Heart Health Study data were used. Mediation analyses, Pearson's correlations, and relative risk (RR) adjusting for age, sex, education, alcohol, smoking, marital status and body mass index were estimated. There are four important findings from this work. First, inflammation, oxidative stress, selected antioxidants, and lifestyle and moderate intensity activity levels contributed to some of the causal relationships between sleep and cardiometabolic health. Second, objective vs. subjective sleep measures correlates moderately but vary by sex, age, education, and obesity. Third, an increase in sleep duration increased the RR of developing hypertension by 29% in a 4 y follow-up. Finally, a decrease in sleep efficiency increased the RR of developing diabetes and dyslipidemia 57% and 65%, respectively. In summary, this work provides evidence that dietary and lifestyle factors lie on the causal pathway of several sleep and cardiometabolic health relationships, and thus explains their importance in cardiometabolic health. It also suggests adults perceive their sleep habits reasonably well, but co-morbidities and demographics affect their perception.

This work also provides evidence that changes in sleep habits in a relatively short time increases the risk of developing hypertension, diabetes, and dyslipidemia. Therefore, optimizing the dietary habits, physical activity levels, and sleep behaviours can improve the cardiometabolic health of adults.

Keywords: Sleep, cardiometabolic health, inflammation, oxidative stress, antioxidants, physical activity, diabetes, hypertension, dyslipidemia, obesity, objective vs. subjective sleep

Dedication

I dedicate this dissertation to my amazing mom, supportive Vava aunty, and the loving memory of my father. Their support and guidance make the successes in my life possible and meaningful. They raised me to be a person with values, to see the beauty in everything, and to stand up for what I believe in. Thank you for teaching me to pursue life with honesty and sincerity, and to handle life with a little dose of humour.

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I would like to thank my family for their support and care of me during my doctoral work. My mom and aunt are truly the ones who made this degree possible. Thank you for believing in me and for giving the freedom to create my own life. I would also like to thank my siblings and their families, especially my nieces, Luxmy and Abina, who ask interesting questions about what I do and make me communicate at their level. Also, my cousins (especially Vitha) and extended family for keeping me sane, and for actually thinking what I do is cool.

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List of Abbreviations

BMI	Body Mass Index
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
GGT	γ-Glutamyl transferase
Glu	Fasting plasma glucose
HDL	High-density lipoprotein cholesterol
Insulin	Fasting insulin concentration
MetS	Metabolic syndrome
MET	Metabolic equivalent
NHANES	National Health and Nutrition Examination Survey
NREM	Non-Rapid Eye Movement
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid Eye Movement
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SBP	Systolic blood pressure
TG	Triglycerides
WC	Waist circumference

Chapter 1 General Introduction

Cardiometabolic Health

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors, primarily obesity, hyperglycemia, dyslipidemia, and hypertension, that elevates the risk of developing cardiovascular disease (CVD), diabetes and certain types of cancers.[1] Specifically, having MetS increases the risk of developing diabetes and cancer by up to 5-fold, and CVD by 2-fold.[2–4] Prevalence of MetS parallels that of obesity; and over a third of US adults have MetS.[5,6] The pathogenesis of MetS is not fully understood, but insulin resistance, chronic inflammation (i.e., inflammatory cytokines), oxidative stress (i.e., reactive oxygen species (ROS) and reactive nitrogen species (RNS)), and reduced antioxidants are associated with MetS.[7–9] Further, research suggests factors associated with modernization, such as reduced sleep, physical inactivity, and unhealthy diet are contributing to the higher prevalence of cardiometabolic conditions.[10–15]

Patterns of Sleep

Changes in sleep patterns are among the many factors that may be contributing to increases in cardiometabolic decline at the population-level. At the most fundamental level, sleep is necessary for maintaining the health of almost all species on earth. However, the duration of sleep has been declining in humans, particularly since the 1960s.[12] Research suggests that the adults in the US slept about 1.5-2 h less in 2002 than in the 1960s.[12] In 2005, US adults reported sleeping 6.8 h on weekdays and 7.4 h on weekends; and the decrease is likely due to societal factors as well as technology use (e.g., shift work, double income families, cable, internet, smartphone, and 24 h access to stores and other conveniences).[16–18] In addition, sleep *quality* has decreased, and both

sleep quality and quantity are essential for maintaining health-related quality of life in humans,[19] and preventing weight gain, abnormal glucose function, hypertension, and hormonal and endocrine dysfunctions.[20]

Factors Protective of Cardiometabolic Health

Protective effects of physical activity and a healthy diet on the risk of developing cardiometabolic conditions are well known.[21] Indeed, poor sleep, physical inactivity, reduced antioxidant capacities, as well as increased systematic inflammation and oxidative stress are common features associated with cardiometabolic decline.[8,9,21–24] However, previous research on cardiometabolic health scarcely considered the connected relationships between physical activity, dietary factors, and sleep habits.[22,24–27]

Conceptual Framework

The factors that influence the relationship between sleep and cardiometabolic health include individual and community level factors, which has the potential to influence sleep habits and alter dietary and physical activity behavoiurs of people, and thus, contribute to cardiometabolic decline (**Figure 1.1**). According to Buxton *et al*.'s[28] framework, sleep deprivation has the potential to induce immediate changes, such as, decrease energy expendure, increase energy intake, increase cortisol levels, and decrease insulin sensitivity, by affecting the energy homeostasis and metabolism of affected individuals. Over time, this can result in clinical and sub-clinical changes, such as a rise in plasma glucose and weight gain, and over longer term this can can lead to the development of chronic cardiometabolic diseases. Within this context, this dissertation estimates the contributions of physical activity and dietary factors (i.e., oxidative stress,

inflammation, antioxidants) to the causal relationship between sleep and cardiometabolic health by evaluating them from a cross-sectional prospective using proxies for cardiometabolic health. Further, the longitudinal relationship between changes in sleep habits and their associated risk for developing cardiometabolic diseases is estimated after adjusting for confounding variables that includes socio-demographic and behavioral factors.

Figure 1.1

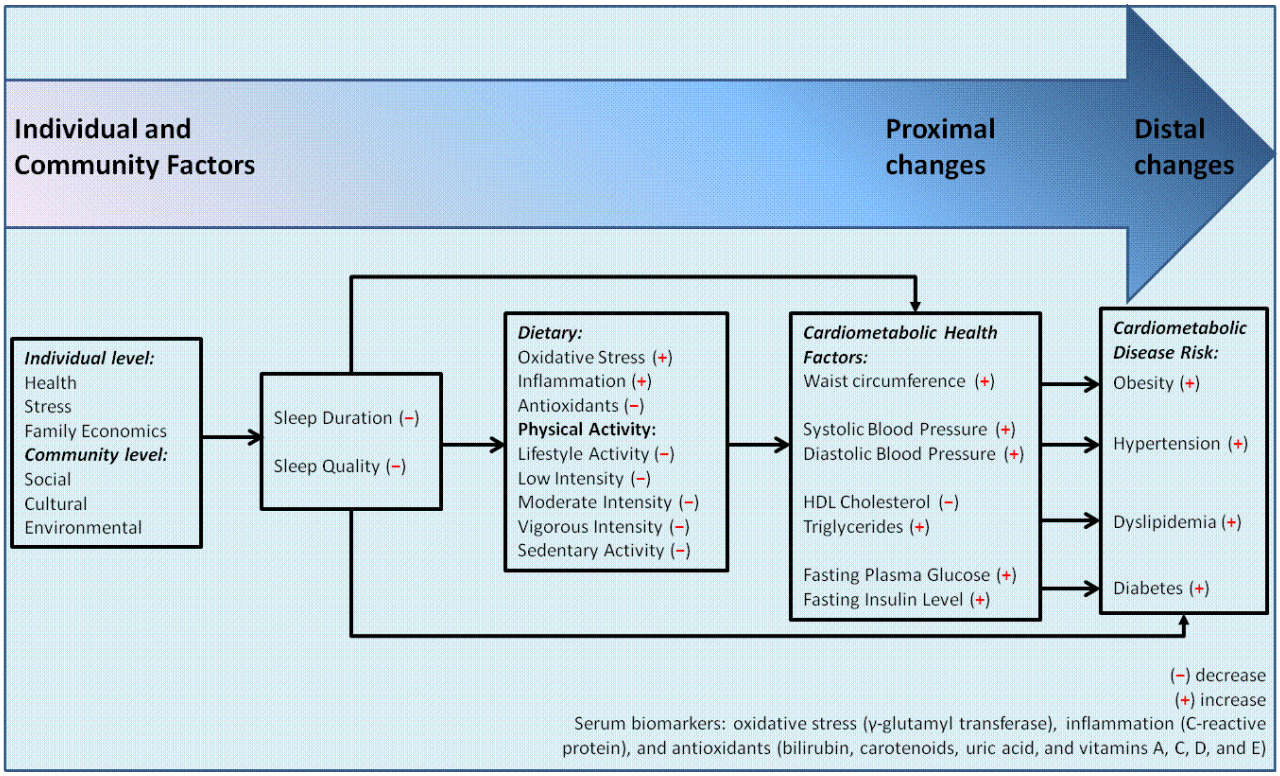


Figure 1.1. The conceptual framework of the factors influencing the relationship between sleep and cardiometabolic health.

The above figure is adapted from Buxton *et al*.[28]

Chapter 2 Literature Review

Sleep and Cardiometabolic Health

The importance of sleep in maintaining optimal cardiometabolic health is well known. Early observational and experimental studies have associated short and long sleep duration as well as poor sleep quality with several cardiometabolic risk factors or MetS.[20,22,29–37] The relationship between MetS and sleep duration is U-shaped, where the optimal sleep of 7 h is associated with the lowest odds of MetS.[38] Studies on sleep and metabolic dysfunction in obstructive sleep apnea patients found continuous positive airway pressure therapy reduced, and in some cases, reversed metabolic dysfunction.[39–42] In fact, the prevalence of metabolic dysfunction is higher in many clinical populations, including obstructive sleep apnea, obesity, diabetes, osteoporosis, arthritis, lung disease, cancer, heart disease, hypertension, and depression.[43] Sleep duration decreases with age, and a significant portion (11%) of the US adults perceive they do not get sufficient sleep.[44]

In 2013, two meta-analyses evaluated the relationship between sleep duration and MetS.[38,45] In the first, Xi *et al*[45] pooled 10 studies (9 cross-sectional and 1 cohort) and found higher odds MetS for short sleep duration (Odds Ratio (OR): 1.27, 95% CI: 1.09-1.47), but not long sleep duration (1.07 (0.87-1.32)). In the second, Ju and Choi[38] also found similar odds of MetS for short sleep duration (OR: 1.27, 95% CI: 1.10-1.48 for cross-sectional and 1.62 (0.74-3.55) for cohort studies) and long sleep duration (1.23 (1.02-1.49) from cross-sectional and 1.62 (0.86-3.04) from cohort studies). These studies provide evidence for a relationship between sleep and cardiometabolic health from an observational perspective.

Inflammation, Oxidative Stress, Antioxidants and Cardiometabolic Health

Chronic inflammation plays a significant role in several diseases, including cancer, MetS, rheumatoid arthritis, asthma, hypertension, neurodegenerative diseases, diabetes and CVD.[46–49] If chronic inflammation is not reduced by endogenous and exogenous antioxidants, it can lead to changes that cause disease.[49] For instance, inflammation as a result of immune cell insults or other endogenous/exogenous stimuli can induce tissue destruction and fibrosis, or lead to other age-related diseases.[49] Aging is associated with decreased immune capacity, decreased antioxidants capacity to combat free radicals, and increased accumulation of free radical damage; although it is not a component of MetS, it is the single greatest non-modifiable risk factor for cardiovascular risk.[46]

A biomarker of inflammation is the C-reactive protein (CRP), which is an acute-phase hepatic protein that is associated with diabetes, MetS, and CVD.[47] γ-glutamyl transferase (GGT) can be used as a diagnostic tool to measure oxidative stress and chronic inflammation.[50] However, the causal pathway between inflammation and oxidative stress is not clear, but it has been hypothesized that elevated GGT precedes CRP in the development of disease.[47] Even within the normal clinical reference range (2-30 U/L), GGT is associated with obesity, diabetes, insulin resistance, blood pressure, non-alcoholic fatty liver, atherosclerosis, and coronary heart disease.[47,50–52] Further, GGT can predict mortality and morbidity, independent of alcohol abuse and liver disease.[50]

Indeed, many studies have found that inflammation and oxidative stress are associated with cardiometabolic decline. For example, Bo *et al*.[47] found a linear association between MetS and CRP/GGT, and these levels were within the current clinical reference range. In Lee *et al*,'s[53] prospective study, GGT activity was increased

in MetS participants, while Onat *et al*.'s [50] prospective cohort study found that GGT was a significant predictor of diabetes, hypertension, and MetS risks. Oxidative stress also inversely relates to endogenous antioxidants, such as bilirubin[52,54] and superoxide dismutase.[55] Bilirubin, for instance, can scavenge peroxyl radicals, and decreases in the serum concentration of bilirubin are associated with CVD, CRP, cardiometabolic decline, obesity and aging.[7,54] In fact, optimal antioxidant levels protect against oxidative stress, and can be found in vitamins A, C, D, and E, and carotenoids.[46,56] Some research suggests that these antioxidants are also decreased in those with MetS.[8,21,56,57]

Emerging research, however, suggests that uric acid, an endogenous antioxidant, is elevated in those with hypertension, diabetes, abdominal obesity, and MetS.[58–66] A diet rich in high-fructose has been associated with the increased serum uric acid levels.[61] From rat studies, Nakagawa *et al*.[67] provided an explanation for the causal role of uric acid in fructose diet-induced, which promotes weight gain, insulin resistance, and dyslipidemia, and thus, causes MetS.[61] Therefore, high fructose diet induces a rise in uric acid levels, and contributes to the cardiometabolic decline in humans.

Dietary Habits, Inflammation, Oxidative Stress, Antioxidants, and Sleep

In populations with sleep disorders, the relationship between inflammation, oxidative stress, antioxidants, and cardiometabolic health is well known.[40,41,68,69] The link between sleep and dietary habits is also known in free-living adults.[24,26,27,70] Indeed, diet is a major influence on one's inflammation, oxidative stress, and antioxidant profile,[71–73] but sleep also has an influence on diet, and thus effects inflammation, oxidative stress, and antioxidant levels.[10] Sleep loss also increases the appetite[74,75] for high fat and high carbohydrate foods.[27,76] Further, reduced sleep duration and quality have been linked to

higher inflammation and oxidative stress level in humans.[9,77,78] In populations with sleep disorders, the dietary consumptions of antioxidant rich foods improves sleep.[79,80] However, the contributions of dietary factors (i.e., inflammation, oxidative stress, and antioxidants) to the relationship between sleep and cardiometabolic health have not yet been quantified.

Physical Activity, Cardiometabolic Health, and Sleep

The beneficial effect of regular physical activity on cardiometabolic health is well known.[13,81–83] Both short and long sleep durations are associated with lower levels of physical activity, but directionally of this relationship is not clear, and several factors, including physical activity may confound the sleep-MetS relationship.[22,25,84,85] Physical inactivity, a common phenomenon in modern societies, is a major health concern.[23,86] In the US, over two third of adults are not meeting the physical activity guidelines,[87] and a linear dose-response relationship between television viewing (a proxy for sedentary time) and cardiovascular events exists.[86] Specifically, physical inactivity is associated with weight gain and obesity, diabetes, hypertension, insulin resistance, and dyslipidemia.[86,88–92] However, research on the relationship between physical activity, sleep, and MetS is limited.[22,93,94]

Objectively Measured and Self-Reported Sleep in Cardiometabolic Health

Beyond the relationships described above, the correlation between objectively measured sleep (e.g. PSG, actigraphy) and self-reported sleep (e.g. questionnaires) is weak-to-moderate and varies across populations.[95,96] Specifically, research on the correlations between objectively measured and self-reported sleep suggests that the correlations are ≤20% in free-living adults,[97] ≤24% in those with sleep apnea,[98] ≤37% in

opioid drug users,[99] and ≤50% in healthy older adults.[100] However, the correlations between objectively measured and self-reported sleep have not yet been adequately studied amongst those with MetS.

To date, only Hall *et al*.[101] studied the correlation between PSG measured and self-reported sleep (Pittsburgh Sleep Quality Index (PSQI)) in participants with MetS. The PSQI collects information on participants usual sleep habits. In this community-based cohort study of White, Chinese, and African American middle-aged women, beta and delta (NREM stage 3/4) activities were inversely correlated with each other (r=-0.27), and with observed slow wave sleep scores (r=-0.26, and r=0.53, respectively).[101] Overall, Hall *et al*.[101] found only a modest correlation between the two methodologies (r <0.20). However, no other studies have evaluated the correction between PSG and self-reported sleep variables in MetS vs. non-MetS population. Further, the correlations studies typically do not use self-reported data on the night of objective sleep measurement, which may affect the correlations in unknown ways.

Finally, most large sleep studies use self-reported sleep data to determine the relationship between sleep and cardiometabolic health,[38] and thus, are susceptible to recall and healthy responder biases. Indeed, Young *et al*.[95], for instance, found that despite reporting poor sleep, postmenopausal women had a more deep sleep (i.e., NREM stages 3/4) than premenopausal women. They also found postmenopausal women slept more than their premenopausal counterpart (388 vs. 374 min, p=0.05).[95,102] While self-reported sleep studies in general support that sleep duration and quality decreases with age, objectively measured sleep research suggests this difference is modest.[97] Therefore, evidence suggests that the correlation between objectively measured and self-

reported sleep varies by measurement tools, sleep variables, and disease, but this relationship has not yet been adequately studied amongst those with MetS, and other subgroups.

Change in Sleep Habits and Cardiometabolic Health

There is evidence to suggest that humans have comprised on our sleep requirements in the last century.[12,103] There is also evidence to suggest that poor sleep may be an important contributor to the rise in metabolic syndrome, diabetes, obesity, and cardiovascular disease.[20,104,105] However, little research has been done on the changes in sleep habits and their associated cardiometabolic disease risk.[106] Several studies used baseline self-reported sleep data to provide evidence for the relationship between sleep deprivation and cardiometabolic dysfunction.[75,107–112] To our knowledge, only one large study has evaluated the relationship between *changes in sleep duration* and its effect on diabetes risk.[106] In this study, Ferrie and colleagues[106] found that an increase in self-reported sleep duration by ≥2 h in a 5 y follow-up increased the risk of diabetes by 50%. Further, most large studies tend to focus on the relationship between *sleep duration* and cardiometabolic health[38] while emerging evidence suggests that *sleep quality* is just as important for cardiometabolic health.[25] Therefore, the relationship between longer-term changes in objectively measured sleep habits (i.e., both sleep duration and quality measures) and their associated cardiometabolic risks warrants immediate study.

Summary, Objectives, and Hypotheses

Considering only a fraction of US the adults (32%) ever consult their physician about sleep habits, but spend billions on sleep aids,[44] further research in this area is needed to understand primary prevention opportunities that may improve human health.

Indeed, research suggests that sleep and cardiometabolic health are independently affected by dietary and physical activity,[24,25,70,103,113,114] but the mediating effect of these factors to the overall relationship between sleep and cardiometabolic health has not yet been considered. Therefore, there is a need to quantify the contributions of lifestyle factors, such as diet and physical activity, and determine whether they lie on the causal pathways of the relationship between sleep and cardiometabolic health. Quantifying the mediatory effect of these factors is a crucial step towards understanding the nuances of this relationship.[10,103,115] To evaluate this research problem (research questions 1), data for this dissertation will be drawn from a rich population-level dataset: the US National Health and Nutrition Examination Survey (Appendix D:.[116] Findings from this work will help develop population-level primary prevention targets, such as sleep hygiene, nutrition, and physical activity-related health promotion activities.

A further issue with existing sleep research is the low reliability of self-reported sleep data, which is often the only type of data available to assess the link between sleep and cardiometabolic health.[102] Additionally, emerging evidence suggests varying sleep habits and cardiometabolic risks in selected groups, e.g., Blacks, women, and older adults, but these subpopulations may also perceive their sleep very differently.[97,101,117–119] Therefore, it is important to estimate the relationship between objective vs. self-reported sleep measures and determine if the requisite sleep habits vary significantly between subgroups.[120] Finding answers to this question will help develop assessment tools that may be used for clinical and research purposes.[95,97,120] Thus, research question 2 of this dissertation will evaluate the relationship between objective vs. subjective sleep

in adults and assesses their variations in subpopulations using a single-night of home-PSG and self-reported sleep data from the Sleep Heart Health Study (Appendix D:.[121]

Finally, the importance of longer-term changes in sleep habits and their associated cardiometabolic disease risks have seldom been studied due to the lack of available longitudinal data.[106,111,122] Most studies on the relationship between sleep and cardiometabolic risks also use self-reported baseline sleep data to predict the risk of cardiometabolic diseases, and thus, they fail to directly relate the higher risks with sleep habits.[16,30,108,109,111,123,124] Therefore, estimating the relationship between changes in objective sleep habits in a follow-up period and their associated cardiometabolic disease risks will help provide stronger evidence and augment our understanding of the temporal relationship between sleep and cardiometabolic health. Research question 3 of this dissertation will make use of objective, longitudinal data from the Sleep Heart Health Study (Appendix D: to address this gap.[121] Evidence from this work may be used to implement policy changes related to sleep hygiene, e.g., exposure to light exposures during the night through street lamps, technology use, and shiftwork.[125–127]

Therefore, the overall purpose of this work is to address the knowledge gaps identified above, and thus, the three key research questions evaluated in this dissertation are:

1. How much do dietary and lifestyle factors contribute to the causal relationship between sleep and cardiometabolic health?
2. How does self-reported and objectively measured sleep correlate in those with MetS?
3. Do changes in sleep habits increase cardiometabolic disease risks?

These research questions are investigated in five distinct manuscripts, as follows:

Manuscript 1:

Objective 1: To explore the interrelationship between sleep duration and inflammation, oxidative stress, and antioxidant capacities.

H1: Optimal inflammation, oxidative stress, and antioxidant levels will be found amongst those who report a sleep duration of 7 to 8 hours per night.

Objective 2: To quantify the indirect mediating effect of these factors on the sleep duration–cardiometabolic health relationships in free-living adults.

H2: Inflammation, oxidative stress, and antioxidants will lie on the causal pathway of the relationships between sleep duration and cardiometabolic risk factors.

H3: Inflammation, oxidantive stress, and antioxidants will contribte to the relationships at least moderately (indirect mediation effect (ab) ≥0.09).

Manuscript 2:

Objective 1: To explore the interrelationship between sleep quality and inflammation, oxidative stress, and antioxidant capacities.

H1: Optimal inflammation, oxidative stress, and antioxidant levels will be found amongst those who report an overall good sleep quality.

Objective 2: To quantify the indirect mediating effect of these factors on the sleep quality–cardiometabolic health relationships in free-living adults.

H2: Inflammation, oxidative stress, and antioxidants will lie on the causal pathway of the relationships between sleep quality and cardiometabolic risk factors.

H3: Inflammation, oxidative stress, and antioxidants will contribute to the relationships at least moderately (i.e., ab ≥0.09).

Manuscript 3:

Objective 1: To estimate the contributions of objectively measured activity levels to the causal relationship between sleep and cardiometabolic health.

H1: Objectively measured activity levels will lie on the causal pathway of the relationships between sleep and cardiometabolic risk factors.

H2: Physical activity levels will contribute to the relationships at least moderately (i.e., ab ≥0.09).

Objective 2: To determine if higher intensities of activity have greater influence, similar to a dose-response relationship.

H3: Higher intensity of physical activity will contribte to the relationships to a greater extent than lower intensities.

Manuscript 4:

Objective 1: To compare measured sleep patterns with self-reported length and quality in people with and without MetS.

H1: At least a modest correlation (r≥0.25) between objectively measured and self-reported sleep will be found amongst those with and without MetS will exist.

Objective 2: To identify whether there are differences in these relationships between subgroups of the population (i.e. male vs. female, age groups, socioeconomic and behavioral factors, and body mass index (BMI) categories).

H2: The correlations will significantly vary between the above subgroups

Objective 3: To quantify the relationship between objectively measured sleep duration and quality with age, sex, MetS, and BMI.

H3: Reductions in objectively measured sleep parameters will significantly result in higher the odds of having MetS or obesity independent of each other, and after adjusting for age and sex.

Manuscript 5:

Objective 1: To estimate the risk of developing hypertension, diabetes, dyslipidemia and obesity following changes in home polysomnography (PSG) measured sleep duration and efficiency.

H1: Changes in objectively measured sleep duration or sleep efficiency by ≥5% will increase the relative risk of developing hypertension, diabetes, dyslipidemia and obesity.

Objective 2: To characterize changes in total sleep time and sleep efficiency over the follow-up.

H2: From baseline and follow-up, both objectively measured sleep duration and sleep efficiency would have decreased

Objective 3: To determine if any differences exist in disease status as a result of changes in sleep habits by disease status.

H3: Those who developed a cardiometabolic disease will have significantly reduced sleep habit between baseline to follow-up compared to those who did not develop the disease.

Chapter 3 Manuscript 1: Contribution of Inflammation, Oxidative Stress, and Antioxidants to the Relationship between Sleep Duration and Cardiometabolic Health

This manuscript was published in the journal of ***Sleep*** and the reprint of it can be found in **Appendix A**. Co-author of this manuscript is Chris Ardern. Thirumagal Kanagasabai and Chris Ardern designed the study, and critically revised the manuscript. Thirumagal Kanagasabai performed the statistical analyses and wrote the manuscript.

Citation: Kanagasabai, Thirumagal, and Chris I. Ardern. “Contribution of Inflammation, Oxidative Stress, and Antioxidants to the Relationship between Sleep Duration and Cardiometabolic Health.” *Sleep* 38, no. 12 (2015): 1905–12.

Chapter 4 Manuscript 2: Inflammation, Oxidative Stress, and Antioxidants Contribute to Selected Sleep Quality and Cardiometabolic Health Relationships: A Cross-sectional Study

This manuscript was published in the journal of ***Mediators of Inflammation*** and the reprint of it can be found in **Appendix B**. Co-author of this manuscript is Chris Ardern. Thirumagal Kanagasabai and Chris Ardern designed the study, and critically revised the manuscript. Thirumagal Kanagasabai performed the statistical analyses and wrote the manuscript.

Citation: Kanagasabai, Thirumagal, and Chris I. Ardern. “Inflammation, Oxidative Stress, and Antioxidants Contribute to Selected Sleep Quality and Cardiometabolic Health Relationships: A Cross-Sectional Study.” *Mediators of Inflammation* 2015 (2015): 824589.

Chapter 5 Manuscript 3: Physical activity is on the casual pathway and contributes to the relationship between sleep and cardiometabolic health: An accelerometer-based assessment in NHANES 2005-06

The co-authors of this manuscript are Chris Ardern and Michael Riddell. Thirumagal Kanagasabai and Chris Ardern designed the study. Chris Ardern and Michael Riddell critically revised the manuscript. Thirumagal Kanagasabai performed the statistical analyses and wrote the manuscript.

Abstract

OBJECTIVE: To estimate the contributions of objectively measured activity levels to the causal relationship between sleep and cardiometabolic health.

RESEARCH DESIGN AND METHODS: Data from the 2005-06 US National Health and Nutritional Examination Survey were used (N=1,226) after excluding for age (<20 y), pregnancy, missing sleep or cardiometabolic health variables, and invalid accelerometer data. Activity thresholds (counts per minute) were sedentary activity (0–99), light intensity (100–759), lifestyle activity (760–2019), moderate intensity (2020–5996), and vigorous intensity (≥5999). The bootstrap method was used to estimate the amount of mediation or contribution of activity levels to the sleep–cardiometabolic health relationships, which were quantified as large (≥0.25) or moderate (≥0.09).

RESULTS: Lifestyle activity level lies on the causal pathway of several sleep duration and cardiometabolic health relationships, most notably for waist circumference (WC), systolic blood pressure (BP), and fasting insulin concentration. Light intensity activity level also moderately contributed to the sleep duration–WC relationship. Moderate intensity, moderate & vigorous intensity, and lifestyle activity levels moderately contributed to the sleep quality–WC, and sleep quality–systolic BP relationships. Finally, moderate intensity and lifestyle activity levels were large contributors to the sleep quality–fasting insulin concentration relationship.

CONCLUSIONS: Lifestyle activity and moderate intensity activity levels have a large effect on the causal relationship between sleep and cardiometabolic health, including WC, BP, and fasting insulin concentration. Therefore, promoting these activities is an important intervention strategy to improve the cardiometabolic health of adults.

Introduction

Sleep deprivation and poor sleep quality compromise the cardiometabolic health of both younger and older adults.[25,113] While the optimal sleep duration for health is controversial, observational studies suggest that people who sleep 7-8 hours per night have higher levels of physical activity,[17] lower levels of sedentary activity,[128] and better cardiometabolic health[114] and antioxidant profiles.[129] Indeed, an inverse dose-response relationship between physical activity and cardiometabolic risk has been shown.[130,131] Independent of physical activity level, sedentary behavior time (i.e., excessive sitting) is an emerging concern. In developed countries, over 50% of adults lead a sedentary lifestyle, which is associated with obesity, diabetes, insulin resistance, hypertension, and dyslipidemia.[86] Further, perceived sleep quality affects one's capacity to engage in physical[132] and sedentary activities.[133]

Observational studies support a moderate-to-strong relationship between metabolic syndrome (MetS) and sleep duration, but this relationship may be distorted by socioeconomic and behavioral factors.[38,133] The association between sleep quality and MetS is also affected by similar confounding variables, and greater variability for the associations between sleep quality and MetS have been found.[25,134] Indeed, one analysis suggests that the causal relationship between sleep disturbance and insulin resistance may be moderate and bidirectional.[135]

Despite the evidence for the presence of these relationships, the interrelated relationships between sleep, physical or sedentary activity, and cardiometabolic health in adults are rarely explored. Of note, studies on sleep and cardiometabolic health consider physical activity as a confounding (rather than explanatory) variable,[16,89,93,118,136,137] and

most previous studies on physical activity and cardiometabolic health do not consider sleep in *any* context.[138] Therefore, the extent to which various physical activity levels contribute to the causal sleep–cardiometabolic health relationship is currently unknown. The purpose of our study is to address this knowledge gap, and thus, quantify the contributing role of physical activity levels. In our study, we will use accelerometer-derived, rather than self-reported, physical activity data to minimize recall and healthy responder bias associated with the latter form of data. We hypothesize that activity levels will lie on the causal pathway between sleep and cardiometabolic health, with higher intensities of activity having greater influence, indicating a dose-response relationship.

Methods

Study Design, Setting, and Participants

Data for this analysis was obtained from the US National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional study designed to assess the health and nutritional status of its non-institutionalized civilian population.[116] Approximately 10,000 people are sampled bi-annually. Data are collected from personal interviews, standardized physical examinations, and laboratory samples.[116] NHANES 2005-2006 cycle with an initial sample of 10,348 individuals was used in this study. Subsequent exclusions for age (<20 y), pregnancy, invalid accelerometer data, missing cardiometabolic health variables (i.e., waist circumference (WC) [cm], systolic blood pressure (BP) [mmHg], diastolic BP [mmHg], triglycerides [mM], high-density lipoprotein (HDL)-cholesterol [mM], fasting plasma glucose [mM] and fasting insulin [pM]), and missing sleep data were made in sequence. The final analytic sample was 1,226.

Exposures: Sleep Duration and Quality

The Sleep Disorders Questionnaire was administered to participants aged ≥16 y, who reported their typical sleep habits for the past month.[116] The present analysis used data from those aged ≥20 y. A single question was used to collect sleep duration information: “How much sleep do you usually get on weekdays or workdays?” Response to this question was collected in whole numbers between 1 and 11 h, and truncated at ≥12 h.[116] Based on previous literature, sleep duration was categorized as “very short” (≤4 h), “short” (5–6 h), “adequate” (7–8 h), and “long” (≥9 h) sleepers.[129] Overall sleep quality was determined from the following six questions: “‘How often did you have trouble falling asleep?”; “How often did you wake up during the night and had trouble getting back to sleep?”; “How often did you wake up too early in the morning and were unable to get back to sleep?”; “How often did you feel unrested during the day, no matter how many hours of sleep you had?”; “How often did you feel excessively or overly sleepy during the day?”; and, “How often did you not get enough sleep?”.[116] Responses to these questions [0=Never; 1=Rarely (1 time a month); 2=Sometimes (2-4 times a month); 3=Often (5-15 times a month); and, 4=Almost always (16-30 times a month)] were summed to obtain an overall sleep quality score.[116,136,139] The sleep quality score was subsequently categorized as: “good” (0 to <3); “fair” (3 to <7); “poor” (7 to <12); and, “very poor” (≥12 to 24).[136,139]

Outcomes: Cardiometabolic Health

Metabolic syndrome (MetS), an indicator of cardiometabolic health, was defined according to the Joint Interim Statement[140] as ≥3 of elevated WC (men: ≥102 cm; women: ≥88 cm), elevated triglycerides (≥1.69 mM) or medication; low HDL cholesterol (men: <1.04 mM; women: <1.29 mM) or medication; elevated BP (systolic: ≥130 mmHg;

diastolic ≥85 mmHg) or medication; and elevated fasting plasma glucose (≥5.6 mM) or medication.[140] Subsequently, these criteria were summed to create a *number of MetS components* [0, 1, 2, 3, 4, 5] variable.[129] Finally, fasting insulin concentration [pM], as well as each MetS component listed above were used as individual outcome variables.

Mediators: Physical Activity and Sedentary activity behaviour

Objective measures of movement intensity and duration were collected over 7 consecutive days (AM-7164, ActiGraph, Walton Beach, FL, USA).[116] Because the ActiGraph monitors were not water-proof, participants were instructed to wear the device on the waist during all waking activities that were non-water-related.[116,141] We obtained the downloadable file from NHANES that contained valid accelerometer data, defined as a wear time of ≥10 h per day for 4 days.[116] Physical activity monitor data was subsequently used to define thresholds for activity in counts per minute (cpm): 0 to 99 for sedentary activity, 100 to 759 for light intensity activity, 760 to 2019 for lifestyle activity, 2020 to 5998 for moderate intensity activity, and 5999 or more for vigorous intensity activity.[141]

Mediation Model

The mediation model, a causal model that explains the underlying relationship between an exposure and an outcome variable through a third (mediatory) variable, was used to estimate the contributions of physical activity levels on the sleep–cardiometabolic health relationship.[142] Briefly, the mediation model is a series of regression analyses that contains four path analyses: 1) path *a* is a regression between exposure and mediator; 2) path *b* is a regression between mediator and outcome while adjusting for the exposure; 3) path *c* is a regression between exposure and outcome; and 4) path *c'* is a regression

between exposure and outcome while adjusting for the mediator.[142] In the mediation model, the products of *ab* and *c-c'* are mathematically equivalent, and *ab* is considered as the "amount" of mediation or contribution a mediator provides to the relationship between an exposure and an outcome.[142]

Demographic and Behavioral Characteristics

Demographic variables used to describe the sample include age, sex, ethnicity, income, and education. Age was further categorized as 20 to <40 y, 40 to <65 y, and ≥65 y. Ethnicity was self-ascribed and categorized as Non-Hispanic White, Non-Hispanic Black, Mexican American, and Other. Income was categorized as <$20,000, $20,000-44,999, and ≥$45,000, and education as <high school, high school, and college. Alcohol intake was categorized as none, <3, and ≥3 drinks per day, and smoking history as current (if smoking now), past (if smoked ≥100 cigarettes in one's life but not a current smoker) or never (if smoked <100 cigarettes in one's life) categories. [129]

Statistical Analyses

Mean and 95% confidence interval (CI) for continuous variables, and frequency (percentage) and 95% CI for categorical variables were determined by sleep duration and sleep quality. ANOVA and χ^2 tests were used, as appropriate, to test for any differences in demographic and behavioral characteristics across groups. The medical exam sample weight from the demographics data file was used to weight descriptive analyses.[116] For the mediation analysis, we used the bootstrap method with 5000 iterations to estimate the amount of mediation or contribution (*ab*) by each mediator, and present the bias corrected *ab* estimates with 95% CI, and p-values.[143] The contribution of each mediator is also described as "large" (≥0.25), "moderate" (≥0.09), "modest" (≥0.01), and "weak"

(<0.01), based on the recommendations of Kenny.[142] All analyses were conducted in SAS v9.3 (Cary, NC, USA), except when the outcome was binary (i.e. MetS). As per the recommendation of Hayes[144] mediation analyses for MetS were conducted using SPSS v22 (Chicago, IL, USA). Statistical significance was set at an α of 0.05.

Results

Demographic and Behavioral Characteristics

The tables provide descriptive information about the US adult population by sleep duration (**Table 5.1**) and sleep quality (**Table 5.2**) categories. While those aged 40–65 y were more frequently short and very short sleepers (**Table 5.1**), the age distribution for long sleep duration was evenly dispersed. Men tended to report shorter sleep durations, but these sex differences became non-existent amongst adequate sleepers and widened for long sleepers (i.e., more women tended to report long sleep duration). The ethnic disparity between sleep durations was also remarkable: non-Hispanic Blacks had a higher proportion of short and very short sleepers, whereas non-Hispanic Whites had a higher proportion of adequate and long sleepers. Higher educational attainment was also less likely, but current smoking was *more* likely, amongst very short sleepers. As expected, a greater proportion of those reporting shorter sleep duration also reported lower sleep quality.

For sleep quality, although 40–65 year olds were more likely to report poor and very poor sleep quality (**Table 5.2**), they were also more likely to report good and fair sleep quality compared to younger and older participants. In men and women, the pattern of sleep quality distribution was similar to sleep duration: men reported good sleep quality and women reported very poor sleep quality. Sleep quality was also self-reported as

higher amongst non-Hispanic Blacks and Mexican Americans compared with Non-Hispanic Whites, whereas lower sleep quality was found in those with more education, as well as regular drinkers and smokers. Sleep duration and quality were also positively related in that very poor quality sleep was associated with a higher proportion of short and very short duration sleep, while good, fair and poor sleep were all associated with adequate sleep duration.

Estimates of Mediations or Contributions

Figure 5.1 and **Figure 5.2** provide the estimates of mediation or contribution by each mediatory variable to the sleep–cardiometabolic health relationships. **Figure 5.1** describes the *sleep duration*–cardiometabolic health relationships. Estimates for moderate intensity, moderate & vigorous intensity, and vigorous intensity activity levels are provided on **Figure 5.1(a);** and, those for lifestyle activity, light intensity, and sedentary activity levels are provided on **Figure 5.1(b)**. Only lifestyle activity and light intensity activity levels had significant contributions on several sleep duration–cardiometabolic health relationships. For the sleep duration–WC relationship, the contributions of lifestyle activity and light intensity activity levels were large and moderate, respectively (*ab* estimate (95% CI), p-value: 0.29 (0.09, 0.54), p=0.01; and, 0.14 (0.04, 0.33), p=0.05, respectively). Similarly, the contributions of lifestyle activity and light intensity activity levels on the sleep duration–systolic BP relationship were large and moderate: 0.37 (0.11, 0.72), p=0.01; and, 0.12 (0.01, 0.32), p=0.11, respectively. Lifestyle activity level also moderately contributed to the relationship between sleep duration and diastolic BP: -0.16 (-0.36, -0.048), p=0.04. Finally, the contributions of lifestyle activity and light intensity activity levels on the sleep duration–fasting insulin concentration

relationship were large: 0.86 (0.30, 1.81), p=0.03; and, 0.59 (0.13, 1.58), p=0.06, respectively.

Figure 5.2 describes the *sleep quality*–cardiometabolic health relationships. Contribution estimates for moderate intensity, moderate & vigorous intensity, and vigorous intensity activity levels are provided on **Figure 5.2(a);** and, those for lifestyle activity, light intensity, and sedentary activity levels are provided on **Figure 5.2(b)**. Overall, the contributions of moderate intensity, moderate & vigorous intensity, and lifestyle activity levels on the sleep quality–WC relationship were moderate: 0.20 (0.05, 0.38), p=0.02; 0.19 (0.04, 0.37), p=0.03; and 0.16 (0.03, 0.31), p=0.03, respectively. Similarly, the same activity measures moderately contributed to the association between sleep quality and systolic BP: 0.19 (0.06, 0.39), p=0.02; 0.19 (0.04, 0.39), p=0.03; and 0.24 (0.06, 0.48), p=0.02, respectively. Similar to its contribution to the relationship between *sleep duration* and diastolic BP, lifestyle activity level also moderately contributed to the relationship between *sleep quality* and diastolic BP: -0.11 (-0.24, -0.03), p=0.03. More importantly, the contributions of moderate intensity, moderate & vigorous intensity, and lifestyle activity levels on the sleep quality–fasting insulin concentration relationship were large: 0.47 (0.11, 1.02), p=0.04; 0.46 (0.08, 1.00), p=0.05 (not significant); and, 0.48 (0.10, 1.05), p=0.04, respectively.

Discussion

Main findings

Our aim was to quantify the contributions of activity levels to the various sleep–cardiometabolic health relationships, and thus, determine whether activity levels lie on the causal pathway. We also aimed to determine if the contributions were dose-

dependent. In these regards, we found that moderate intensity, moderate & vigorous intensity, light intensity, and lifestyle activity levels significantly contributed to the relationship between sleep and WC, and sleep and BP. To our surprise, moderate intensity and lifestyle activity levels had a large contribution to the sleep–fasting insulin concentration relationship, while higher intensity activities did not. Thus, the contributions of activity levels to the sleep–cardiometabolic health relationships were not dose-dependent. To our knowledge, this is the first time that the contributions of activity levels on the sleep–cardiometabolic health relationship have been evaluated, several of which warrant discussion.

Waist Circumference

The independent association between self-reported sleep disturbances or physical inactivity and elevated WC is generally moderate.[93] Our finding that activity levels significantly contributed to the sleep–WC relationship is consistent with this work, but our lack of finding for a dose-dependent influence by the various activity levels contrasts some previous work.[130,131] The narrow scope of our analysis (i.e., we evaluated the contributions of activity levels to the sleep–WC relationship), and the use of a cross-sectional dataset to evaluate causal relationships[122] may partially explain this discrepancy. Nonetheless, the richness of the NHANES dataset allowed us to provide initial evidence for the causal relationships on which future work can build. Further, it is important to note that we used the bootstrap method, which is a nonparametric test that assumes linear relationships between paths,[143] and thus, our estimates are likely *conservative*.

Our estimates for the contribution of lifestyle activity and light intensity activity levels (i.e., comparable to non-exercise activity thermogenesis (NEAT)) on the sleep–WC relationship is novel. Previously, NEAT was found to be lower amongst those living with obesity,[145] while its relationship with sleep was speculative.[146] It is still unclear to what extent obesity is attributed to the overall decrease in metabolic rate, including NEAT-based energy expenditure, but some research suggests that obesity is associated with increased sleeping metabolic rate[137] and nocturnal activity counts.[118] The increased sleeping metabolic rate may be due to increased sympathetic activity during nocturnal hours.[147] However, NHANES required participants to remove the accelerometer during sleep, and thus, it is unlikely that the bed time activity counts had an effect on our findings.[116] Indeed, the complex relationship between sleep, nocturnal activities, obesity, and cardiometabolic health is an area of research that needs further study. Future studies should use accelerometer-based sleep and physical activity data to limit the biases associated with self-reports.

Blood Pressure Control

Our findings suggest that within the sleep–BP framework, any contributing effects of physical activity levels are moderate. This is consistent with other studies that found only weak-to-moderate correlations between physical activity intensity and nocturnal BP.[89] Still, another accelerometer-based study found no association between lifestyle activity level and BP,[138] while a recent meta-analysis found that exercise only reduces BP modestly.[148] Being physically active, however, influences the nocturnal dipping of BP through the sympathetic and renin–angiotensin systems.[89] Therefore, our study provides evidence that moderate and lifestyle activities are important contributors to the causal

relationship between sleep and blood pressure. However, further research is needed to clarify the relationship between physical activity intensity, sleep, and blood pressure.

Glycemic Control

Several plausible mechanisms explain the relationship between sleep deprivation and insulin resistance, including the rise in evening cortisol levels, and the decrease in non-insulin-dependent utilization of glucose in the brain.[149] Higher energy expenditure, however, is beneficial for insulin sensitivity and glycemic control in diabetes and pre-diabetes, as it offers opportunities to utilize glucose through insulin-dependent pathways.[149,150] The low-to-moderate physical activity also has an acute blunting effect on insulin levels,[151] but physical activity is seldom considered in studies on sleep and insulin resistance or glycemic control.[16,136] In this respect, our finding that moderate intensity and lifestyle activity are large contributors to the relationship between sleep and fasting insulin concentration addresses an existing knowledge gap. From a clinical perspective, promoting sleep alongside moderate intensity or lifestyle activity is likely to have a beneficial effect on the insulin sensitivity of patients.

Finally, evidence for moderate associations between specific sleep habits and impaired glycemic control exists;[136] however, longitudinal evidence suggests only a modestly elevated diabetes risk amongst short sleepers, after adjusting for self-reported baseline physical activity levels.[16] In line with this, our results suggest that activity level did not significantly alter the relationship between sleep and fasting plasma glucose. Several measurement issues may have contributed to this (null) finding, including the narrow homeostatic range of plasma glucose in the non-diabetic and medicated diabetic populations.[152] Innate differences between the types of glucose tests have also been

found to moderate the relationship between physical activity and glycemic control, i.e., a dose-dependent association between physical activity and 2 h post-challenge plasma glucose, but not fasting plasma glucose, exists.[153] We were unable to use the 2 h post-challenge plasma glucose in our study as it was only performed in a subsample (i.e., ~50% of the sample).[116] Future studies using the Homeostatic model assessment (HOMA) indices for insulin resistance and β cell function may provide additional information on the contributions of activity levels to the broader sleep–glycemic control relationship.

Our work raises an additional question: Can sleep deprivation be compensated by increased physical activity levels to yield the same cardiometabolic health benefits of an adequate sleeper? If so, what physical activity intensities and volumes are needed to compensate for the sleep deprivation? Answering these questions in adult samples will help inform guidelines on the joint promotion of sleep, physical activity, and sedentary time, similar to those that are in development for children.[115] Additionally, dietary factors including micronutrients are important contributors to the sleep–cardiometabolic health relationships.[129,139]

Strengths and limitations

There are several strengths and limitations associated with our study. First, given the cross-sectional nature of the design, future longitudinal studies are needed to confirm and augment our findings. Second, in applying our study exclusion criteria, our final analytic sample was only a fraction of the initial adult sample, but all analyses were bootstrapped with replacement, which provided conservative, bias-corrected indirect effect estimates. Although physical activity measures were accelerometer-based, sleep

measures were self-reported and susceptible to recall and response bias. There are also some notable limitations to the use of accelerometer data, including the possibility that data could be lost due to device tampering or processing, that it records only uniaxial movement, and the novelty of wearing the device may result in higher activity levels.[154] Finally, all behavioral measures in our study are susceptible to change, and with baseline-only assessments, we were unable to account for this.

Conclusions

This study shows that moderate intensity and lifestyle activity levels, but not vigorous intensity or sedentary time, explain the causal relationships of sleep–WC, sleep–BP, and sleep–fasting insulin concentration. Thus, promoting these activities is a possible intervention strategy to improve the cardiometabolic health of adults. Since physical activity and sleep are related behaviours, intervening at the physical activity level may also positively influence sleep habits.

Table 5.1. Characteristics of the US adult population ≥20 years of age by sleep duration

Characteristics		Sleep Duration per Night				p-value
		Very Short (n=65)	Short (n=407)	Adequate (n=665)	Long (n=89)	
Age (Mean (95% CI))		48.0 (43.6, 52.5)	48.6 (47.0, 50.2)	48.9 (46.4, 51.4)	50.6 (46.5, 54.8)	NS
Age categories (% (95% CI))						
	20 to <40 years	24.5 (8.4, 40.6)	28.3 (23.0, 33.6)	32.1 (27.1, 37.0)	33.2 (21.3, 45.1)	
	40 to <65 years	65.0 (48.9, 81.1)	56.8 (50.4, 63.2)	48.5 (44.5, 52.6)	37.8 (20.1, 55.6)	<0.05
	≥65 years	10.5 (3.7, 17.3)	14.9 (9.7, 20.0)	19.4 (13.6, 25.2)	28.9 (18.1, 39.8)	
Sex						
	Men	57.1 (33.7, 80.4)	53.0 (47.7, 58.3)	50.2 (45.8, 54.6)	34.5 (25.2, 43.8)	NS
	Women	42.9 (19.6, 66.3)	47.0 (41.7, 52.3)	49.8 (45.4, 54.2)	65.5 (56.2, 74.8)	
Ethnicity						
	Non-Hispanic White	60.6 (48.3, 73)	64 (55.3, 72.7)	76.7 (70.8, 82.6)	80.8 (72.5, 89.1)	
	Non-Hispanic Black	21.5 (11.2, 31.8)	16.1 (10.1, 22)	6.4 (3.3, 9.5)	6.9 (3.3, 10.5)	<0.05
	Mexican American	7.9 (4.3, 11.6)	8.3 (5.5, 11.1)	7.7 (5.3, 10.2)	5.4 (2.3, 8.6)	
	Others	9.9 (0.0, 23.0)	11.6 (7.0, 16.2)	9.2 (5.8, 12.6)	6.9 (0.2, 13.5)	
Education						
	< High school	23.5 (15.5, 31.6)	16.6 (10.3, 22.8)	14.2 (9.5, 19.0)	12.3 (5.7, 18.9)	
	High school	39.7 (21.8, 57.6)	27.4 (23.7, 31.2)	24.1 (19.9, 28.2)	24.7 (16.8, 32.6)	<0.05
	College	36.8 (18.1, 55.5)	56.0 (49.8, 62.1)	61.7 (54.5, 68.9)	63.0 (50.5, 75.6)	
Income						
	<$20,000	24.3 (12.9, 35.7)	13.7 (8.9, 18.6)	11.7 (8.5, 14.9)	19.1 (9.6, 28.6)	
	$20,000-44,999	24.4 (17.3, 31.5)	27.6 (20.7, 34.5)	29.4 (22.8, 35.9)	31.6 (20.8, 42.5)	NS
	≥$45,000	51.2 (38.7, 63.8)	58.7 (48.4, 69.0)	59.0 (51.4, 66.5)	49.2 (36.5, 62.0)	
Smoking						
	None	38.1 (23.0, 53.2)	49.5 (42.7, 56.4)	49.4 (43.6, 55.1)	63.3 (54.8, 71.8)	
	Current	49.0 (38.4, 59.5)	25.1 (16.9, 33.4)	18.9 (13.7, 24.1)	19.6 (10.2, 29.0)	<0.05
	Past	12.9 (2.0, 23.8)	25.3 (20.2, 30.5)	31.7 (26.5, 36.9)	17.1 (8.2, 26.0)	
Alcohol Intake						

	0 drinks per day	38.4 (27.7, 49.2)	35.6 (29.4, 41.8)	30.0 (26.3, 33.8)	36.4 (21.5, 51.4)	
	<3 drinks per day	36.0 (25.7, 46.3)	44.1 (35.8, 52.4)	45.8 (41.1, 50.5)	48.7 (33.5, 63.9)	NS
	≥3 drinks per day	25.6 (11.4, 39.8)	20.3 (14.1, 26.4)	24.2 (20.6, 27.7)	14.9 (7.1, 22.7)	
Sleep Quality						
	Good	0.8 (0.0, 2.6)	10.7 (6.1, 15.4)	18.7 (14.0, 23.4)	21.4 (14.6, 28.3)	
	Fair	9.3 (1.1, 17.5)	16.9 (12.8, 21.0)	29.4 (24.7, 34.2)	28.0 (14.9, 41.0)	<0.05
	Poor	13.3 (4.7, 21.9)	32.8 (25.0, 40.5)	36.4 (31.2, 41.6)	35.3 (20.9, 49.7)	
	Very Poor	76.5 (65.5, 87.6)	39.6 (31.3, 48.0)	15.5 (11.6, 19.3)	15.3 (7.5, 23.1)	

Mean (95% CI) for continuous variables and frequency % (95% CI) for categorical variables. Sleep Duration are very short (≤4 h per night), short (5–6 h per night), adequate (7–8 h per night), and long (≥9 h per night). Responses to six sleep quality habits were summed and categorized as quartiles as good (<3), fair (≥3 to 7), poor (≥7 to 12), and very poor (≥12). $p<0.05$, two-sided; ANOVA or χ^2, as appropriate. NS is not significant. Sum of weights = 57,869,978.

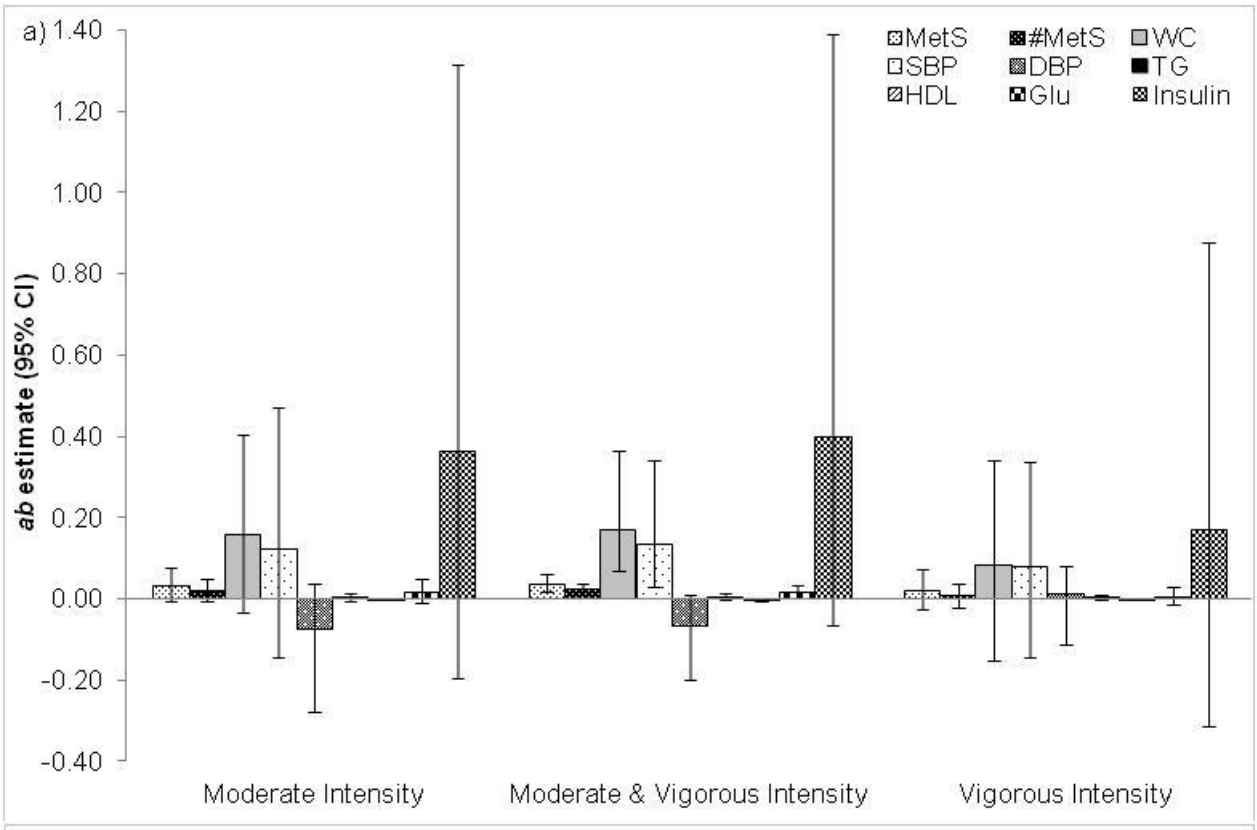
Table 5.2. Characteristics of the US adult population ≥20 years of age by sleep quality

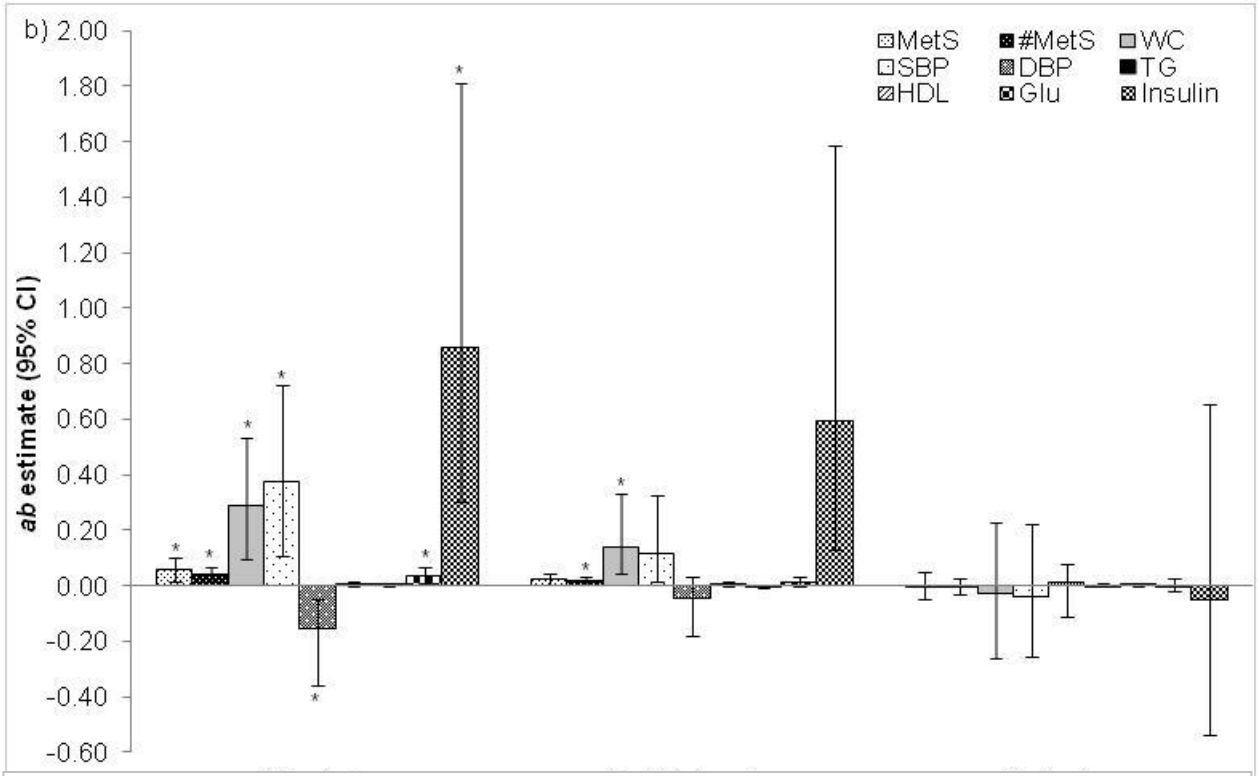
Characteristics		Sleep Quality				p-value
		Good (n=256)	Fair (n=292)	Poor (n=366)	Very poor (n=312)	
Age (Mean (95% CI))		52.2 (49.3, 55.2)	48.7 (46.0, 51.3)	48.2 (46.1, 50.3)	48.0 (45.6, 50.4)	NS
Age categories (% (95% CI))						
	20 to <40 years	26.2 (18.0, 34.4)	34.1 (26.5, 41.7)	30.1 (26.5, 33.8)	30.7 (23.3, 38.0)	
	40 to <65 years	48.1 (39.8, 56.4)	45.8 (36.6, 54.9)	53.5 (49.7, 57.4)	55.0 (45.2, 64.7)	<0.05
	≥65 years	25.7 (18.1, 33.4)	20.1 (14.7, 25.6)	16.3 (11.4, 21.2)	14.4 (8.4, 20.3)	
Sex						
	Men	63.9 (56.1, 71.7)	50.1 (42.2, 58.0)	48.7 (43, 54.5)	44.4 (37.1, 51.8)	<0.05
	Women	36.1 (28.3, 43.9)	49.9 (42, 57.8)	51.3 (45.5, 57.0)	55.6 (48.2, 62.9)	
Ethnicity						
	Non-Hispanic White	59.4 (46.9, 71.9)	73.2 (64.6, 81.8)	76.6 (66.8, 86.3)	73.5 (67.6, 79.4)	
	Non-Hispanic Black	13.4 (6.8, 20.1)	9.3 (4.9, 13.7)	7.9 (4.5, 11.2)	11.9 (7.3, 16.4)	<0.05
	Mexican American	15.8 (9.2, 22.3)	7.4 (3.8, 10.9)	5.8 (3.4, 8.2)	5.9 (3.9, 7.9)	
	Others	11.4 (5.1, 17.7)	10.1 (3.3, 16.8)	9.7 (3.3, 16.1)	8.7 (4.7, 12.8)	
Education						
	< High school	25.1 (18.0, 32.1)	17.1 (9.8, 24.5)	10.6 (6.8, 14.4)	13.8 (10.2, 17.3)	
	High school	26.1 (18.6, 33.6)	22.3 (17.3, 27.4)	26.2 (21.1, 31.4)	28.7 (24.3, 33.2)	<0.05
	College	48.8 (37.3, 60.4)	60.5 (52.3, 68.8)	63.1 (55.7, 70.6)	57.5 (52.4, 62.6)	
Income						
	<$20,000	15.6 (11.1, 20.2)	14.7 (9.0, 20.4)	9.9 (6.4, 13.3)	15.6 (10.4, 20.8)	
	$20,000-44,999	33.5 (24.3, 42.8)	29.2 (21.6, 36.9)	28.2 (19.4, 36.9)	26.1 (19.8, 32.5)	NS
	≥$45,000	50.8 (41.6, 60.1)	56.1 (47.5, 64.6)	62.0 (51.9, 72.0)	58.3 (49.8, 66.8)	
Smoking						
	None	50.7 (40.1, 61.3)	47.1 (38.5, 55.6)	54.4 (48.1, 60.6)	45.9 (37.6, 54.2)	
	Current	21.2 (11.7, 30.8)	19.5 (13.5, 25.6)	17.9 (11.8, 24.0)	31.5 (24.8, 38.2)	<0.05
	Past	28.0 (19.3, 36.7)	33.4 (24.8, 42.0)	27.7 (21.6, 33.9)	22.6 (17.0, 28.3)	
Alcohol Intake						

	0 drinks per day	38.7 (30.9, 46.4)	33.2 (25.6, 40.9)	29.4 (22.1, 36.6)	32.5 (26.1, 38.9)	
	<3 drinks per day	38.8 (30.1, 47.5)	46.6 (38.3, 54.8)	47.3 (39.8, 54.8)	44.2 (36.6, 51.9)	NS
	≥3 drinks per day	22.5 (15.7, 29.3)	20.2 (16.9, 23.5)	23.3 (18.3, 28.4)	23.3 (18.1, 28.4)	
Sleep Duration						
	Very Short	0.3 (0.0, 0.8)	1.9 (0.0, 3.9)	1.9 (0.4, 3.5)	14.7 (9.9, 19.5)	
	Short	21.0 (13.5, 28.6)	20.9 (13.9, 28.0)	29.3 (24.3, 34.3)	46.7 (35.9, 57.5)	<0.05
	Adequate	69.4 (60.8, 78.1)	69.5 (62.2, 76.7)	61.8 (54.3, 69.3)	34.6 (25.4, 43.9)	
	Long	9.3 (5.3, 13.3)	7.7 (5.0, 10.4)	7.0 (2.5, 11.5)	4.0 (1.3, 6.6)	

Mean (95% CI) for continuous variables and frequency % (95% CI) for categorical variables. Responses to six sleep quality habits were summed and categorized into quartiles as good (<3), fair (≥3 to 7), poor (≥7 to 12), and very poor (≥12). Sleep Duration are very short (≤4 h per night), short (5–6 h per night), adequate (7–8 h per night), and long (≥9 h per night). $p<0.05$, two-sided; ANOVA or χ^2, as appropriate. NS is not significant. Sum of weights = 57,869,978.

Figure 5.1





Activity Level

Figure 5.1. The contribution of a) moderate, moderate & vigorous, and vigorous activities, b) lifestyle activity, light, and sedentary activity activities on the sleep duration–cardiometabolic health relationship

MetS. metabolic syndrome; #MetS, number of MetS components; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL, high-density lipoprotein cholesterol; Glu, fasting plasma glucose; Insulin, fasting insulin concentration; *ab* estimate, amount of mediation or contribution by the mediatory variable; CI, confidence interval. *p<0.05, 95% CI are bias-corrected, bootstrapped values.

Figure 5.2

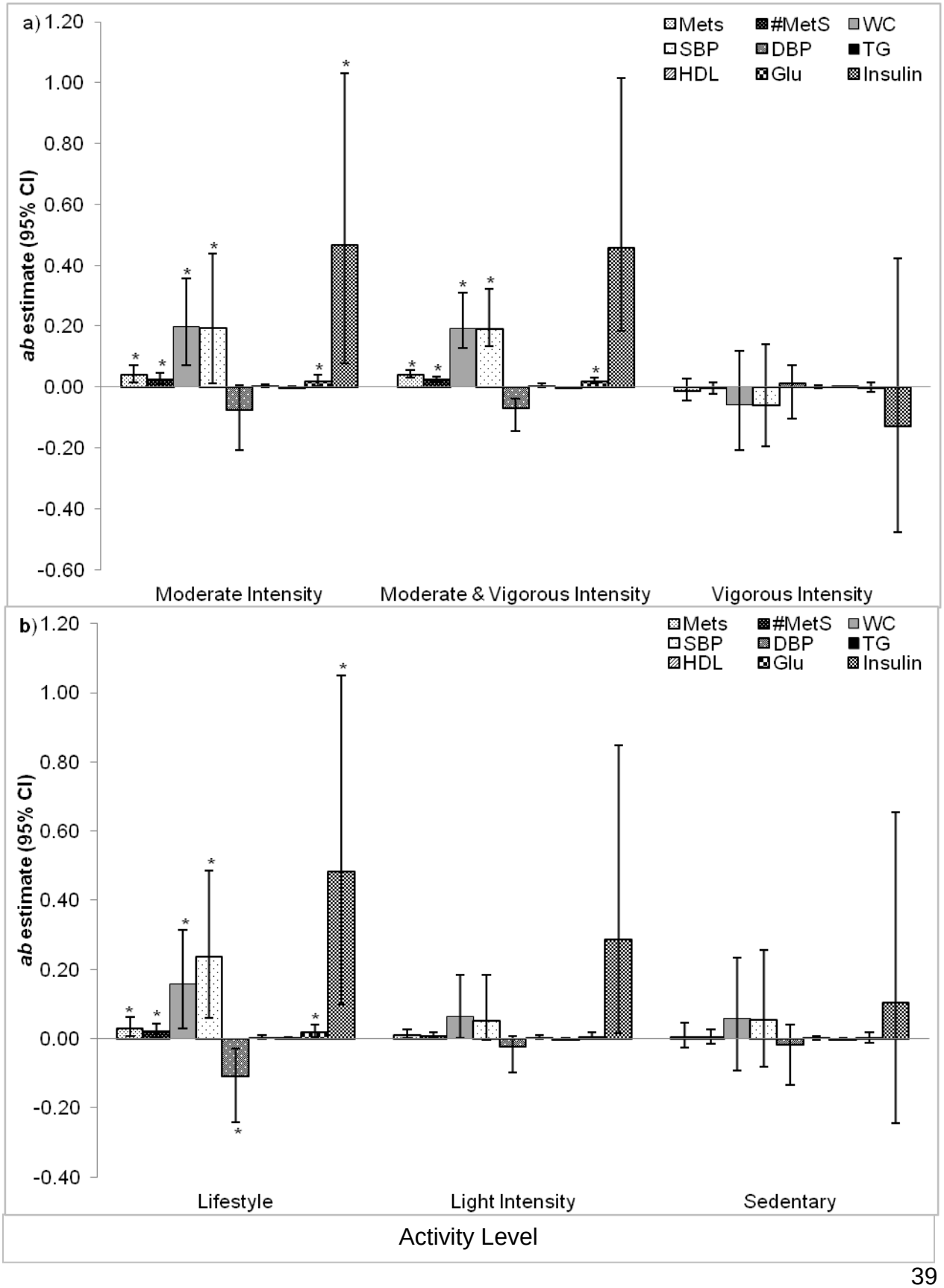

a)
b)
Mets
#MetS
WC
SBP
DBP
TG
HDL
Glu
Insulin
ab estimate (95% CI)
1.20
1.00
0.80
0.60
0.40
0.20
0.00
-0.20
-0.40
-0.60
Moderate Intensity
Moderate & Vigorous Intensity
Vigorous Intensity
Lifestyle
Light Intensity
Sedentary
Activity Level

Figure 5.2. The contribution of a) moderate, moderate & vigorous, and vigorous activities, b) lifestyle activity, light, and sedentary activity activities on the sleep quality–cardiometabolic health relationship

MetS. metabolic syndrome; #MetS, number of MetS components; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL, high-density lipoprotein cholesterol; Glu, fasting plasma glucose; Insulin, fasting insulin concentration; *ab* estimate, amount of mediation or contribution by the mediatory variable; CI, confidence interval. *p<0.05, 95% CI are bias-corrected, bootstrapped values.

Chapter 6 Manuscript 4: Objective and Subjective Measures of Sleep, and the relationship between Sleep, Obesity, and Metabolic Syndrome: A cross-sectional study

The co-authors of this manuscript are Chris Ardern and Alison Macpherson. Thirumagal Kanagasabai and Chris Ardern designed the study. Chris Ardern and Alison Macpherson critically revised the manuscript. Thirumagal Kanagasabai performed the statistical analyses and wrote the manuscript.

Abstract

Study Objectives: 1) To compare measured sleep patterns with self-reported length and quality in people with and without MetS; 2) to identify whether there are differences in these relationships between subgroups of the population (i.e. male vs. female, age groups, socioeconomic and behavioral factors, and body mass index (BMI) categories); and, 3) to quantify the relationship between objectively measured sleep duration and quality with age, sex, MetS, and BMI.

Design: Cross-sectional analysis of the Sleep Heart Health Study 1995-1998 exam cycle.

Setting: Multi-cohort study with non-probability samples of US residents.

Participants: Age ≥39 y with valid home-polysomnography (PSG), self-reported sleep and cardiometabolic health data (N=5,204).

Interventions: N/A.

Measurements and Results: Objective vs. subjective sleep measures correlate moderately (r=0.27–0.48) and vary by subgroups (r=0.25–0.56). Having both MetS and obesity was associated with 9.41 min and 5.76 min less PSG measured sleep duration after adjusting for age, sex, and BMI or MetS. Being overweight or obese was the strongest predictor of MetS, while objectively measured sleep duration, efficiency and latency contributed minimally.

Conclusions: This study found that adults perceive sleep habits reasonably well, but co-morbidities and demographics affect their perception. Living with obesity reduces sleep duration and quality, and being overweight or obese increases the odds of MetS.

Keywords: Objective vs. Subjective Sleep, Correlations, Obesity, Metabolic Syndrome, Sleep Duration, Sleep Efficiency, Sleep Latency

Introduction

Obtaining sufficient sleep on a regular basis is necessary for maintaining cardiometabolic health of humans.[155] Seven to 8 h of sleep per night is associated with the lowest metabolic syndrome (MetS) prevalence, and shorter sleep durations worsen the cardiometabolic health of both adults and children.[38,75] Some evidence also suggests a relationship between sleep quality and cardiometabolic health. [25,134] However, sleep quality is inconsistently defined, which makes it difficult to compare studies.[108]

Additionally, most large sleep studies use self-reported sleep information, and thus, they are susceptible to healthy responder bias. Indeed, systematic over-reporting of sleep duration is common, but over-reporting also varies in subpopulations. [102] Lauderdale and *et al*.,[102] for instance, found that 5 h sleepers over-reported sleep duration by 1.2 h compared to actigraphy data; 7 h sleepers over-reported sleep duration by 0.4 h. Research also suggests perceived sleep varies across the lifespan.[97] One study suggests postmenopausal women get more sleep and better quality sleep than premenopausal women,[95] while ageing is a commonly accepted reason for declining sleep duration and quality.[97] Other studies have also found that the correlation between objectively measured (e.g. polysomnography (PSG), actigraphy) and self-reported sleep (e.g. questionnaires) is weak-to-moderate.[98–100] To date, only Hall *et al.*[101] studied the correlation between PSG measured and self-reported sleep variables ($r<0.20$) in participants with MetS. However, this study compared objectively sleep measures with participants' usual sleep habits rather than the night during which the objective measures were collected.[101] This appears to be a common practice in sleep research, and it may

be an inaccurate representation of the correlation between objective vs. subjective sleep measures.

Although the relationship between MetS and obesity, as well as sleep habit is well known,[38,74,75,140] yet large studies using objectively measured sleep to evaluate the simultaneous relationship with MetS and obesity are rare.[101] Objectively measured sleep duration and quality are, however, reduced in those with MetS[101] and obesity.[118]. In Hall *et al*.'s [101] study, obesity was considered as a confounding variable, and they found that the associations between MetS and sleep efficiency, Non-Rapid Eye Movement (NREM) stage 1, or Apnea-Hypopnea Index (AHI) remained significant independent of obesity in middle-aged women. Indeed, the simultaneous relationship between objectively measured sleep parameters, obesity and MetS remains to be elucidated in the general adult population.

Therefore, the objectives for this study are 1) to compare measured sleep patterns with self-reported length and quality in people with and without MetS; 2) to identify whether there are differences in these relationships between different populations (i.e. male vs. female, age groups, socioeconomic and behavioral factors, as well as body mass index (BMI) classes); and, 3) to quantify the relationship between objectively measured sleep duration and quality with age, sex, MetS, and BMI classes. With regards to the first two objectives, we hypothesize at least a modest correlation ($r \geq 0.25$) between objectively measured and self-reported sleep amongst those with and without MetS, as well in subpopulations. With regards to the third objective, we hypothesize that reductions in objectively measured sleep parameters will significantly increase the odds of having MetS or obesity independent of each other.

Methods

Participants

To assess our hypotheses, we accessed the Sleep Heart Health Study (SHHS) data through sleepdata.org, courtesy of the National Sleep Research Resource.[121] The US National Heart, Lung, and Blood Institute funded SHHS, which contains de-identified information on participants from six individual studies: Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, Strong Heart Study, New York Hypertension Cohorts, Tucson Epidemiologic Study of Airways Obstructive Diseases and the Health and Environment Study. The SHHS dataset contains information on participants (initial n=6,441) age ≥39 y, whose sleep and cardiometabolic information were collected during two follow-up periods (1995-1998 and 2001-2003). For this analysis, only data from 1995-1998 was used (n=5,804). We excluded participants without reliable REM/NREM data (n=85) or missing cardiometabolic health variables (i.e., waist circumference, triglycerides, systolic and diastolic blood pressures, HDL cholesterol, diabetes status) for a final analytical sample of 5,204. Ethics approval was obtained from York University (Toronto, Canada), and was submitted to National Sleep Research Resource to gain data access.

Sleep variables

Home-PSG-derived sleep measures includes time in REM (original variable name: scremp), NREM stage 1 (scstg1p), NREM stage 2 (scstg2p), NREM stage 3/4 (scstg34p), total sleep time (slp_time), sleep latency (slp_lat), sleep efficiency (slp_eff), time in bed (time_bed), WASO (wake after sleep onset, waso) and arousal Index (ai_all). Subjectively measured sleep variables came from the sleep habits questionnaire and the morning

survey. Sleep habits questionnaire variables were Epworth Sleepiness Scale (ess_s1), time to fall asleep (mi2slp02), weekday sleep time (hrswd02), weekend sleep time (hrswe02), trouble falling asleep (tfa02), unrested days (funres02), waking up too early (wu2em02), waking up during night (wudnrs02), not enough sleep (nges02), use of sleeping pills (tkpill02), and overly sleepy (sleepy02). The morning survey variables were total sleep time (60 x hwlghr10 + hwlgmn10), time to sleep (minfa10), sleep restful (rest10), sleep quality (hwwell10), and difficulty falling asleep (diffa10). In the manuscript, we have superscripted PSG for home-PGS and MS for morning survey to indicate the tool used to collect the specific sleep variable.

Metabolic syndrome

We used a modified version of the Joint Interim Statement for MetS[140] because fasting glucose information was not available in the pooled dataset. The diagnostic cut-offs were: 1) elevated waist circumference (original variable name: waist, ≥102 cm (Men) and ≥88 cm (Women)), 2) elevated triglycerides (trig, ≥1.69 mM) or the use of medications indicated for dyslipidemia, 3) low HDL cholesterol (hdl, <1.04 mM (Men) and <1.29 mM (Women)), 4) and, elevated blood pressure (systbp, ≥130 mmHg (systolic), or diasbp, ≥85 mmHg (diastolic)) or the use of medications indicated for hypertension.[140] *In lieu* of elevated fasting plasma glucose (≥5.6 mM), we used the history of diabetes (parrptdiab) or the use of medication/insulin indicated for hyperglycemia. Therefore, the presence of ≥3 of the diagnostic cut-offs indicates MetS.

Demographics and Behavioral Characteristics

Age (age_s1), sex (gender), MetS, ethnicity (ethnicity and race), education (educat), alcohol (alcoh), cigarette pack-years (cgpkyr), smoking status (smokstat_s1),

marital status (mstat), body mass index (bmi_s1) were used to describe the sample. Age was categorized as 39-54, 55-64, 65-74, and 75-90 y. The original race variable was categorized as Whites, Blacks, and Others. Using the ethnicity variable, we further identified the ethnic group of Hispanic or Latino, and categorized the remaining participants as Others. Education was categorized based on the number of years in school (≤10, 11-15, 16-20, and >20 y). Alcohol intake (drinks per day) was categorized as none, moderate, and heavy using the sex specific cut-offs (i.e. moderate: ≤2 (Men), and ≤1 (Women); heavy: >2 (Men), and >1 (Women)), as per the dietary guidelines for Americans.[156] The categorization for smoking status (never, current, and former) and marital status (married, widowed, divorced/separated, and never married) were from the data source, while the body mass index (BMI: kg/m^2) was categorized as normal weight (<25), overweight (25 to <30), or obese (≥30).

Statistical Analysis

MetS status and sex stratified mean (95% confidence interval (CI)) for continuous variables, and frequency (n) (%) for categorical variables were determined. T-tests and χ^2 were used, as appropriate, to make between and within group comparisons. Pearson's correlation test was used to estimate the correlation between home-PSG-derived and self-reported sleep variables. To detect a modest correlation of ≥0.25 with 80% power, a sample size of 97 participants is required. Correlation analyses were also stratified by MetS status, sex, age, ethnicity, education, smoking, alcohol, marital status, and BMI to test the same hypothesis. To detect significant differences between subgroups (e.g., men vs women), the z-score for the difference between two correlations was used.[157] From the correlation analyses, the following home-PSG-derived sleep measures were identified

as variables of interest for the subsequent multivariable regression analyses: total sleep^{PSG}, sleep latency^{PSG} and sleep efficiency^{PSG}. β coefficients (95% CI) were estimated in multiple linear regressions that included age, sex, MetS status, and BMI as covariates. Using the same variables, multivariable logistic regressions were performed to estimate the odds for having MetS. All analyses were conducted in SAS v9.3 (Cary, NC, USA) and statistical significance set at an α of 0.05.

Results

Those with MetS were slightly older, less educated, non-drinkers, smoked greater cigarette pack years compared to non-MetS, but smoking status did not significantly differ by MetS status (**Table 6.1**). The prevalence of obesity, men of White ethnicity, women of Black ethnicity, and women in widowhood were higher in the MetS group. Compared to women, men with MetS were younger while non-MetS men were older. Men also reported higher educational attainment, drank and smoked more compared to women. In addition, a higher prevalence of MetS was found in both men and women living with excess body weight.

In general, sleep quantity from the home-PSG, sleep habits questionnaire, and the morning survey were significantly lower amongst those with MetS, while sleep quality was poorer (**Table 6.2**). Women obtained more total sleep^{PSG}, NREM stage 3/4^{PSG} (i.e., deep sleep), and had greater sleep efficiency^{PSG} (i.e., time spent asleep over time spent in bed) compared to men, but women also had greater sleep latency^{PSG} (i.e., time taken to fall asleep). These patterns were similar in the self-reported sleep measures as well.

Figure 6.1 contains the correlations for home-PSG vs. selected morning survey variables (i.e., total sleep time^{MS} and time to sleep^{MS}). We found that total sleep^{PSG}, time in bed^{PSG},

and NREM S2^{PSG} positively correlated with total sleep time^{MS} (**Figure 6.1a**), while sleep efficiency^{PSG} negatively correlated with time to sleep^{MS} (**Figure 6.1b**). The grey shaded area in the graphs is the null hypothesis region (r <0.25). The sleep habits questionnaire variables did not correlate ≥0.25 with any of the home-PSG variables (data not shown). MetS status did not affect participants' ability to perceive total sleep time^{MS}, as the correlation between total sleep time^{MS} and home-PSG variables did not vary by MetS status (**Figure 6.2**a), but the correlations of total sleep time^{MS} vs. total sleep^{PSG} and sleep efficiency^{PSG} were higher in women (**b**). The correlations of total sleep time^{MS} vs. total sleep^{PSG} and time in bed^{PSG} were also greater in younger people (**c**). Those with ≥11 y of education (**d**), not divorced/separated (**e**), or heavy drinkers (**f**) also had higher correlations of total sleep time^{MS} vs. time in bed^{PSG}. Finally, normal weight people perceived sleep duration better than those living with obesity do—the correlation of total sleep time^{MS} vs. total sleep^{PSG} was significantly higher in normal weight people compared to those living with obesity (**g**). The correlations between total sleep time^{MS} and home-PSG variables were not different and ≥0.25 for ethnicity or smoking status (data now shown).

Figure 6.3 contains the correlations between time to sleep^{MS}, an indicator of sleep latency, and home-PSG variables. The correlation between time to sleep^{MS} and sleep efficiency^{PSG} was higher amongst those with MetS (**a**), while the correlation between time to sleep^{MS} and sleep time^{PSG} was negative but higher in women (**b**). Older people (**c**), Blacks (**d**), those with 16-20 y of education (**e**) and heavy drinkers (**f**) had greater correlations between perceived and objective sleep latency (i.e., time to sleep^{MS} and sleep latency^{PSG}). The correlations between perceived and home-PSG sleep latency

variables were not significantly different by marital status, smoking history or BMI classes (data not shown).

Having MetS and obesity was associated with 9.41 m and 5.76 m lower total sleep^{PSG}, respectively, in our mutually adjusted models with age, sex, and MetS and BMI (**Table 6.3**). In these models, having MetS also increased sleep latency^{PSG} and decreased sleep efficiency^{PSG}; being a woman increased both sleep latency and efficiency, and; living with obesity decreased sleep efficiency by approximately 1%. However, being overweight or obese was strongly associated with having MetS after adjusting for age, sex, and BMI (**Table 6.4**). Sex and age also predicted MetS, but total sleep^{PSG}, sleep latency^{PSG} and sleep efficiency^{PSG} had little effect.

Discussion

The primary objective of our study was to determine the correlation between objective vs. subjective measures of sleep. In this regard, we hypothesized that the correlations will be at least modest ($r \geq 0.25$), and that they would vary in subpopulations. We found that selected objective (i.e., total sleep^{PSG}, time in bed^{PSG}, and NREM stage 2^{PSG}) and subjective (total sleep time^{MS}) variables correlated moderately. Similarly, sleep efficiency^{PSG} and sleep latency^{PSG} also moderately correlated with time to sleep^{MS}. These correlations varied amongst some subpopulations: age, sex, MetS, BMI, marital status, ethnicity, education and alcohol intake. Our secondary objective was to quantify the relationship between objectively measured sleep duration (sleep time^{PSG}) and quality (sleep efficiency^{PSG} and sleep latency^{PSG}) with age, sex, MetS, and BMI classes in mutually adjusted models. Our findings suggest that women get more sleep even after adjusting for age, MetS and BMI, but having MetS or living with obesity reduced sleep

time^{PSG}. However, sleep latency^{PSG} was higher in women or those with MetS, while sleep efficiency^{PSG} was lower in those with MetS. On the other hand, living with obesity was associated with the largest odds of having MetS, and sleep had little effect after adjusting for age, sex, and BMI.

Correlations and variations by subpopulations

Our results are consistent with other studies on the correlation between PSG and self-reported sleep.[95,97–102,158] However, most studies compare PSG or objectively measured sleep measures with participants' usual sleep habits—akin to the sleep habits questionnaire data in our study—rather than the self-reported sleep variables based on the night of the objectively measured sleep, and thus, fail to account for the reduction in sleep duration and quality associated with using PSG.[97] Indeed, our correlations between the sleep habits questionnaire variables and home-PSG sleep variables were not ≥0.25, and our data suggests that using PSG reduces even the perceived sleep duration and quality. Therefore, comparing the morning survey variables with home-PSG is a better reflection of the sleep duration and quality obtained during the night of PSG. However, the lower sleep duration and quality during the night of PSG may have reduced participants' ability to perceive sleep.[159]

The novelty of our study also lies in our subpopulation analyses. Women, for instance, in addition to obtaining more sleep, are also more perceptive of their sleep habits, but their ability to perceive sleep may decrease with age.[95] Indeed, women are more likely to over report sleep problems with advancing age, even though advancing age is commonly associated with decreased sleep duration and quality in both sexes.[97] Subjective reporting of sleep is also influenced by the overall health status of the

participants, i.e., healthier subjects have better perceived sleep than their counterparts, and whether they consider their sleep habits as problematic.[159] Therefore, clinicians should use objective tools to track their patients' sleep habits; however, discretion is needed when choosing the appropriate tool: PSG can interfere with the sleep of the participants, and actigraphy is less effective in those with insomnia.[102]

Our finding that time to sleep^{MS} and sleep latency^{PSG} correlated better amongst people of retirement age augments current knowledge that support increased sleep latency with age—a difference of only 10 minutes between 20 and 80 y olds.[160] However, it is not clear why older adults are better able to perceive sleep latency than younger adults. The earlier bed time and napping behavior in older adults may have increased their alertness prior to falling asleep.[161,162] However, cognitive and physical health declines associated with aging may explain the decrease in correlation we found for ≥75 y olds.[163]

It is also not clear why the correlation between time to sleep^{MS} and sleep latency^{PSG} for Blacks and heavy drinkers in our study was better than their counterparts, but sleep architecture is different in African Americans[164,165] and drinkers.[166] Perhaps, the shorter sleep duration associated with these groups[166,167] made them more perceptive of their sleep latency as well. Finally, we found that in some instances time to sleep^{MS} and sleep efficiency^{PSG} also correlated, but this comparison is not appropriate since they are not the same parameter of sleep quality.[168]

Multivariable analyses

Our finding that having MetS or living with obesity reduced total sleep^{PSG} aligns with previous literature on sleep duration and MetS,[38] and obesity.[75] However, the

decrease was only <10 minutes after adjusting for age, sex, obesity or MetS—this small difference was previously unknown, and therefore, our study extends current knowledge. In experimental studies, only subtle changes in endocrine and metabolic health were found when acute sleep curtailment of *hours* were used.[74,149,169] However, sleep studies in general raise an important question regarding the best sleep duration for endocrine and metabolic health. To this end, the recent consensus statement on sleep duration for adults recommends ≥ 7 h of sleep on a regular basis for overall health.[170]

The relationships of sleep quality with MetS and obesity, however, has greater variability.[25,118,134] Therefore, we focused our analyses on sleep latency^{PSG} and sleep efficiency^{PSG}, and found that only small but significant differences exist independent of other factors. This study, however, suggests that sleep efficiency^{PSG}, the percentage of the total time spend sleeping out of the overall time spend in bed, may be more important for MetS and obesity than sleep latency^{PSG} (the time taken to fall asleep). The clinical importance of sleep efficiency vs. sleep latency warrant further study, but exogenous melatonin has been found to shorten sleep latency and thus improve sleep efficiency.[171] Indeed, sleep latency and sleep efficiency are inversely related, which was confirmed in our study as well. Nevertheless, when we flipped the model and evaluated the effect of the PGS-derived sleep variables and their associations with MetS, sleep had little effect on the odds of having MetS, independent of being overweight or living with obesity, age, and sex. Therefore, preventing, managing and treating obesity is likely the best strategy against cardiometabolic decline.

Limitations

An advantage of our study is the richness of the dataset. We had access to both objective and subjective sleep measures, and subjective sleep variables included the typical sleep habits as well as a morning survey. However, the home-PSG data were only collected for 1 night, which may not be an accurate reflection of participants' *usual* sleep duration and quantity. Since our analysis is cross-sectional in nature, we are also unable to assess whether the exposure occurred before the outcome, i.e., we cannot infer causality. Further, the novelty of wearing the PSG may have affected the perceived sleep measures in unknown ways, similar to the effect of wearing accelerometer to collect activity data.[154] Also, other important factors that affect sleep and cardiometabolic health are physical activity and diet, which were not available in this dataset. The dataset is also nearly 2 decades old, and thus, may not be reflective of today's population. Finally, the lab-PSG is considered the gold standard to assess sleep objectively, while our study used home-PSG derived data. However, research suggests only minimal variations between the two methodologies.[172]

Conclusions

Our research found that adults perceive sleep habits reasonably well, but co-morbidities and demographics affect their perception. Living with obesity or having MetS reduces sleep quantity and quality; and, sleep has a significant, but modest, association with MetS after adjusting for age, sex, and obesity. Prospective studies using objective measures of sleep are needed to better understand the relationship between changes in sleep habits and cardiometabolic health.

Table 6.1. Characteristics of the study sample

Characteristics	Non-MetS (n=3,262)			MetS (n=1,942)			
	Men (n=1,541)	Women (n=1,721)	p value[1]	Men (n=878)	Women (n=1,064)	p value[2]	p value[3]
Age (mean (95% CI))	63.7 (63.1, 64.2)	62.5 (61.9, 63.0)	<0.05	64.1 (63.5, 64.8)	66.4 (65.7, 67.0)	<0.05	<0.05
Age category (n (%))							
39-54 y	325 (21.1)	438 (25.5)	<0.05	154 (17.5)	141 (13.3)	<0.05	<0.05
55-64 y	483 (31.3)	566 (32.9)		285 (32.5)	299 (28.1)		
65-74 y	452 (29.3)	410 (23.8)		292 (33.3)	355 (33.4)		
75-90 y	281 (18.2)	307 (17.8)		147 (16.7)	269 (25.3)		
Ethnicity							
White	1320 (85.7)	1446 (84.0)	NS	784 (89.3)	900 (84.6)	<0.05	NS
Black	133 (8.6)	162 (9.4)		43 (4.9)	94 (8.8)		
Hispanic or Latino	56 (3.6)	84 (4.9)		33 (3.8)	56 (5.3)		
Others	32 (2.1)	29 (1.7)		18 (2.1)	14 (1.3)		
Education							
≤10 y	102 (7.1)	107 (6.8)	<0.05	90 (10.8)	118 (11.8)	<0.05	<0.05
11-15 y	630 (43.8)	860 (54.3)		384 (45.9)	626 (62.8)		
16-20 y	601 (41.8)	569 (35.9)		317 (37.9)	239 (24.0)		
>20 y	104 (7.2)	48 (3.0)		46 (5.5)	14 (1.4)		
Alcohol							
None	605 (41.0)	981 (59.9)	<0.05	433 (52.8)	740 (73.4)	<0.05	<0.05
Moderate	246 (16.7)	202 (12.3)		117 (14.3)	79 (7.8)		
Heavy	624 (42.3)	454 (27.7)		270 (32.9)	189 (18.8)		
Cigarette (pack-years)	16.1 (15, 17.2)	8.8 (8, 9.6)	<0.05	21.3 (19.5, 23.1)	10.9 (9.7, 12.2)	<0.05	<0.05
Smoking status							
Never	585 (38.2)	984 (57.5)	<0.05	298 (34.2)	605 (57.0)	<0.05	NS
Current	142 (9.3)	160 (9.4)		86 (9.9)	86 (8.1)		
Former	803 (52.5)	567 (33.1)		487 (55.9)	370 (34.9)		
Marital Status							

Married	1353 (88.3)	1235 (72.6)		778 (89.5)	710 (67.1)		
Widowed	38 (2.5)	203 (11.9)		21 (2.4)	187 (17.7)		
Divorced/Separated	109 (7.1)	213 (12.5)	<0.05	55 (6.3)	131 (12.4)	<0.05	<0.05
Never Married	33 (2.2)	51 (3.0)		15 (1.7)	30 (2.8)		
Body Mass Index							
Normal Weight	472 (30.6)	747 (43.4)		70 (8.0)	171 (16.1)		
Overweight	795 (51.6)	628 (36.5)	<0.05	361 (41.1)	400 (37.6)	<0.05	<0.05
Obese	274 (17.8)	346 (20.1)		447 (50.9)	493 (46.3)		

Mean (95% CI) for continuous variables and n (%) for categorical variables. Alcohol cut-offs are sex-specific (for men heavy is >2 drinks per day, and for women heavy is >1 drink per day). T-test or χ^2, as appropriate between [1]Non-MetS men vs. women, [2]MetS men vs. women, and [3]Non-MetS vs. MetS. NS, not significant. MetS, metabolic syndrome.

Table 6.2. Home Polysomnography, self-reported sleep habits, and the morning survey-based sleep duration and quality measures by MetS status in men and women

	Sleep measure	Non-MetS (n=3,262)		MetS (n=1,942)		p value [1]
		Men (n=1,541)	Women (n=1,721)	Men (n=878)	Women (n=1,064)	
Home-PSG	REM (m), mean (95% CI)	70.3 (68.9, 71.7)	75.1 (73.8, 76.5)*	64.2 (62.4, 66.0)§	68.9 (67.2, 70.7)*§	<0.05
	NREM Stage 1 (m)	21.8 (21.1, 22.6)	15.8 (15.2, 16.3)*	21.5 (20.5, 22.5)	15.8 (15.2, 16. 5)*	NS
	NREM Stage 2 (m)	215.5 (212.8, 218.1)	201.9 (199.2, 204.7)*	214.9 (211.1, 218.6)	192.9 (189.2, 196.5)*§	<0.05
	NREM Stages 3/4 (m)	46.6 (44.8, 48.4)	80.9 (78.9, 83.0)*	45.6 (43.3, 48.0)	78.5 (75.6, 81.2)*	NS
	Total Sleep (m)	352.6 (349.2, 355.9)	369.3 (365.8, 372.8)*	343.5 (338.6, 348.5)§	351.2 (346.2, 356.2)*§	<0.05
	Sleep Latency (m)	20.4 (19.1, 21.7)	22.9 (21.4, 24.5)*	24.7 (22.7, 26.7)§	26.3 (24.5, 28.1)§	<0.05
	Sleep Efficiency (%)	81.2 (80.5, 81.9)	83.3 (82.7, 83.9)*	79.8 (78.9, 80.8)§	80.5 (79.6, 81.3)§	<0.05
	Time in Bed (m)	432.6 (429.7, 435.4)	441.9 (439.2, 444.6)*	429.2 (425.1, 433.3)	434.7 (430.9, 438.4)§	<0.05
	WASO (m)	65.6 (63.8, 67.9)	54.5 (52.6, 56.4)*	68.7 (65.5, 72.0)	62.5 (59.9, 65.1)*§	<0.05
	Arousal Index (n/h)	20.7 (20.1, 21.2)	16.7 (16.3, 17.1)*	23.2 (22.4, 24.1)§	17.9 (17.3, 18.5)*§	<0.05
Self Reported Sleep Habits Questionnaire	Epworth Sleepiness Scale	8.2 (8.0, 8.4)	7.2 (7.0, 7.4)*	8.7 (8.4, 9.0)§	7.3 (7.1, 7.6)*	<0.05
	Time to fall asleep (m)	15.4 (14.5, 16.2)	19.0 (18.0, 19.9)*	15.7 (14.6, 16.8)	22.5 (21.1, 23.8)*§	<0.05
	Weekday Sleep Time (h)	7.0 (7.0, 7.1)	7.0 (7.0, 7.1)	7.1 (7.0, 7.1)	7.0 (6.9, 7.1)	NS
	Weekend Sleep Time (h)	7.4 (7.4, 7.5)	7.5 (7.4, 7.5)	7.5 (7.4, 7.6)	7.3 (7.2, 7.3)*§	<0.05
	Trouble Falling Asleep, n (%)	152 (9.9)	316 (18.4)*	95 (10.8)	250 (23.5)*§	<0.05
	Unrested Days	206 (13.4)	313 (18.2)*	162 (18.5)§	256 (24.1)*§	<0.05
	Waking up too early	216 (14.0)	335 (19.5)*	135 (15.4)	251 (23.6)*§	<0.05
	Waking up during night	242 (15.7)	407 (23.8)*	148 (16.9)	298 (28.0)*§	<0.05
	Not enough sleep	230 (14.9)	346 (20.1)*	144 (16.4)	226 (21.2)*	NS
	Use of sleeping pills	76 (4.9)	166 (9.7)*	48 (5.5)	123 (11.6)*	<0.05
	Overly sleepy	172 (11.2)	205 (11.9)	125 (14.2)§	160 (15.0)§	<0.05

Morning Survey	Total Sleep Time (m)	399.5 (395.3, 403.6)	402.4 (398.1, 406.7)	396 (390.1, 401.9)	392.7 (386.8, 398.7)§	<0.05
	Time to sleep (m)	23.4 (22.0, 24.8)	27.9 (26.1, 29.7)*	25.5 (23.4, 27.7)	33.2 (30.7, 35.7)*§	<0.05
	Sleep Restful	202 (13.1)	287 (16.7)*	157 (17.9)§	181 (17.0)	<0.05
	Sleep Quality	172 (11.2)	211 (12.3)	115 (13.1)	132 (12.4)	NS
	Difficulty falling asleep (yes)	419 (27.8)	506 (30.1)	257 (29.9)	376 (36.0)*§	<0.05

Mean (95% CI) for continuous variables and n (%) for categorical variables. For the self-reported sleep habits questionnaire, n (%) is for reporting often (5-15 times per month) and almost always (16-30 time per month). For the morning survey, n(%) is for reporting restless and somewhat restless for sleep restful, or worse and somewhat worse than usual for sleep quality. T-test or χ^2, as appropriate. *p<0.05 within group comparison (Non-MetS or MetS) by sex. [1]Overall group comparison between Non-MetS vs. MetS. §Between group comparison (Non-MetS and MetS) by men and women. NS, not significant. MetS, metabolic syndrome.

Table 6.3. Mutually adjusted multivariable models predicting change in total sleep, sleep latency and sleep efficiency

	β coefficient (95% CI)		
	Total Sleep^{PSG} (m)	**Sleep Latency^{PSG} (m)**	**Sleep Efficiency^{PSG} (%)**
Age	-1.08 (-1.27, -0.90)*	0.04 (-0.04, 0.11)	-0.24 (-0.28, -0.21)*
Women	13.75 (9.76, 17.73)*	2.10 (0.48, 3.72)*	1.54 (0.83, 2.25)*
MetS	-9.41 (-13.83, -5.00)*	3.45 (1.66, 5.23)*	-1.19 (-1.98, -0.40)*
Overweight	1.23 (-3.68, 6.14)	-0.61 (-2.59, 1.37)	0.29 (-0.58, 1.15)
Obese	-5.76 (-11.36, -0.16)*	0.74 (-1.53, 3.01)	-1.06 (-2.06, -0.07)*

Models predict the unit change in total sleep^{PSG}, sleep latency^{PSG}, and sleep efficiency^{PSG}. Referents were men, Non-MetS, and Normal Weight. *p<0.05

Table 6.4. Mutually adjusted multivariable models estimating the odds MetS for total sleep, sleep latency and sleep efficiency

	OR_{MetS} (95% CI)		
Total Sleep^{PSG} (m)	1.00 (1.00, 1.00)	-	-
Sleep Latency^{PSG} (m)	-	1.01 (1.00, 1.01)	-
Sleep Efficiency^{PSG} (%)	-	-	0.99 (0.98, 1.00)
Age	1.03 (1.02, 1.03)	1.03 (1.02, 1.04)	1.03 (1.02, 1.04)
Women	1.22 (1.05, 1.42)	1.24 (1.06, 1.45)	1.28 (1.09, 1.50)
Overweight	3.07 (2.51, 3.77)	2.83 (2.29, 3.51)	2.83 (2.29, 3.51)
Obese	9.07 (7.31, 11.24)	8.69 (6.92, 10.91)	8.62 (6.87, 10.82)

Modeling the odds of MetS for total sleep^{PSG}, sleep latency^{PSG}, and sleep efficiency^{PSG}. Referents were men and Normal Weight. *p<0.05. All OR (odds ratios) were significant.

Figure 6.1

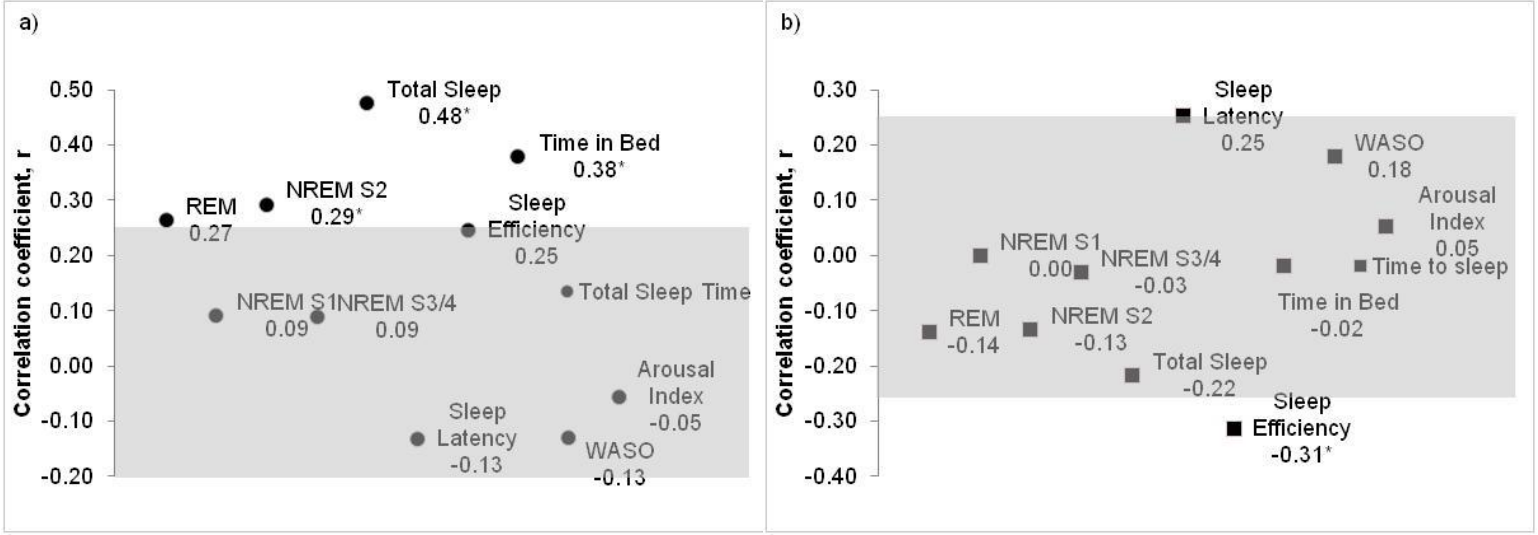


Figure 6.1. Correlations between home-polysomnography-derived sleep measures and the morning survey-based variables total sleep time (a) and time to sleep (b).

*p<0.05 for H_1 ($r \geq \pm 0.25$). Gray shaded area indicates $-0.25 \leq r \geq 0.25$.

Figure 6.2

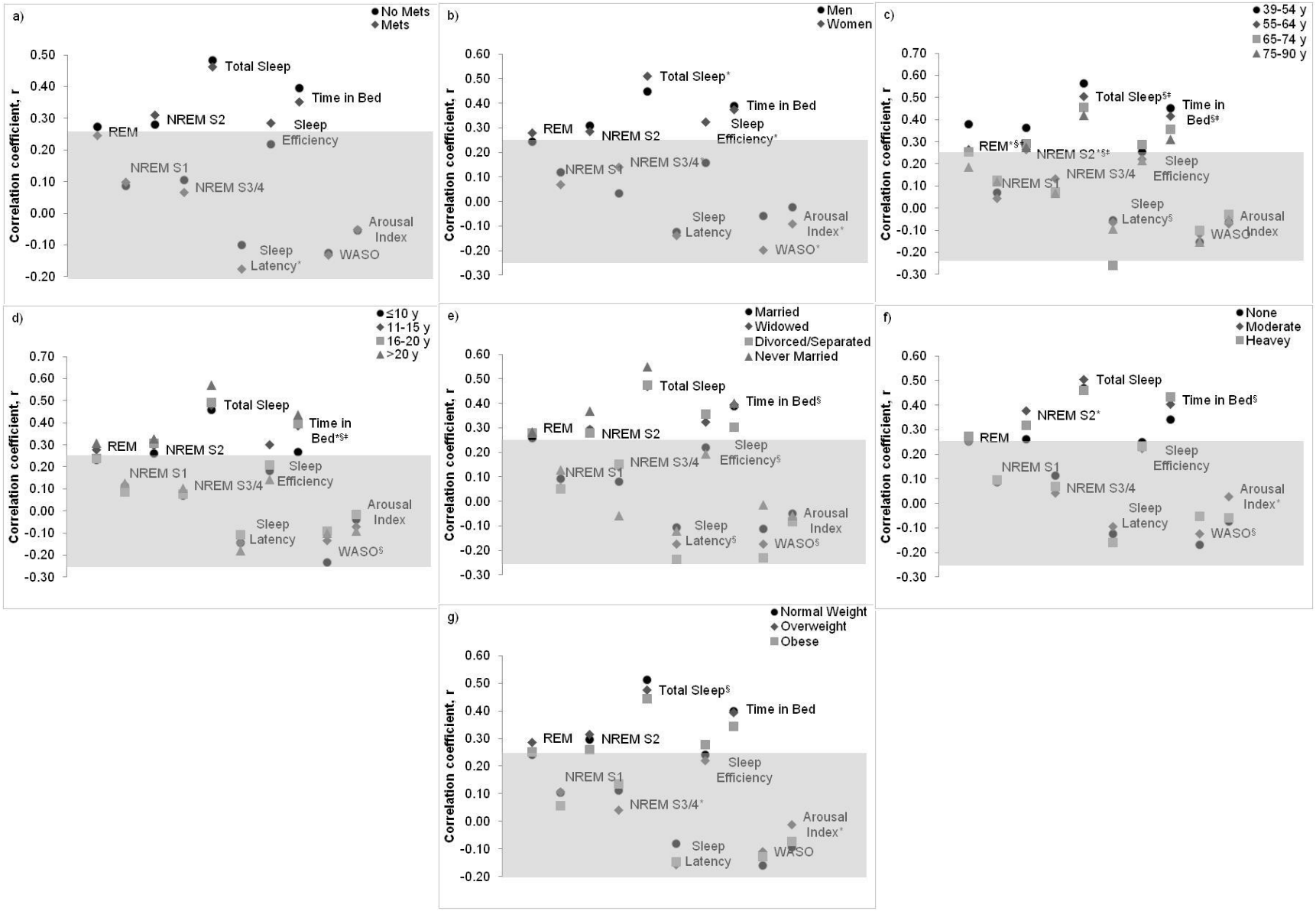

a)
No Mets
Mets
Correlation coefficient, r
Total Sleep
Time in Bed
REM
NREM S2
Sleep Efficiency
NREM S1
NREM S3/4
Arousal Index
Sleep Latency*
WASO
b)
Men
Women
Total Sleep*
Time in Bed
REM
NREM S2
Sleep Efficiency*
NREM S1
NREM S3/4
Sleep Latency
Arousal Index*
WASO*
c)
39-54 y
55-64 y
65-74 y
75-90 y
Total Sleep§‡
Time in Bed§‡
REM*§†
NREM S2*§‡
NREM S1
NREM S3/4
Sleep Efficiency
Sleep Latency§
Arousal Index
WASO
d)
≤10 y
11-15 y
16-20 y
>20 y
Total Sleep
Time in Bed*§‡
REM
NREM S2
NREM S1
NREM S3/4
Sleep Efficiency
Sleep Latency
Arousal Index
WASO§
e)
Married
Widowed
Divorced/Separated
Never Married
Total Sleep
Time in Bed§
REM
NREM S2
NREM S1
NREM S3/4
Sleep Efficiency§
Sleep Latency§
Arousal Index
WASO§
f)
None
Moderate
Heavey
Total Sleep
Time in Bed§
NREM S2*
REM
NREM S1
Sleep Efficiency
NREM S3/4
Arousal Index*
Sleep Latency
WASO§
g)
Normal Weight
Overweight
Obese
Total Sleep§
Time in Bed
REM
NREM S2
Sleep Efficiency
NREM S1
NREM S3/4*
Arousal Index*
Sleep Latency
WASO

Figure 6.2. Correlation between home-polysomnography-derived sleep measures and the morning survey-based variable total sleep time stratified by MetS (a), sex (b), age (c), education (d), marital status (e), alcohol consumption (f) and BMI classes (g).

*p<0.05 for first and second group; §p<0.05 for first and third group; and, ‡p<0.05 for first and fourth group. MetS is metabolic syndrome, and BMI is body mass index.

Figure 6.3

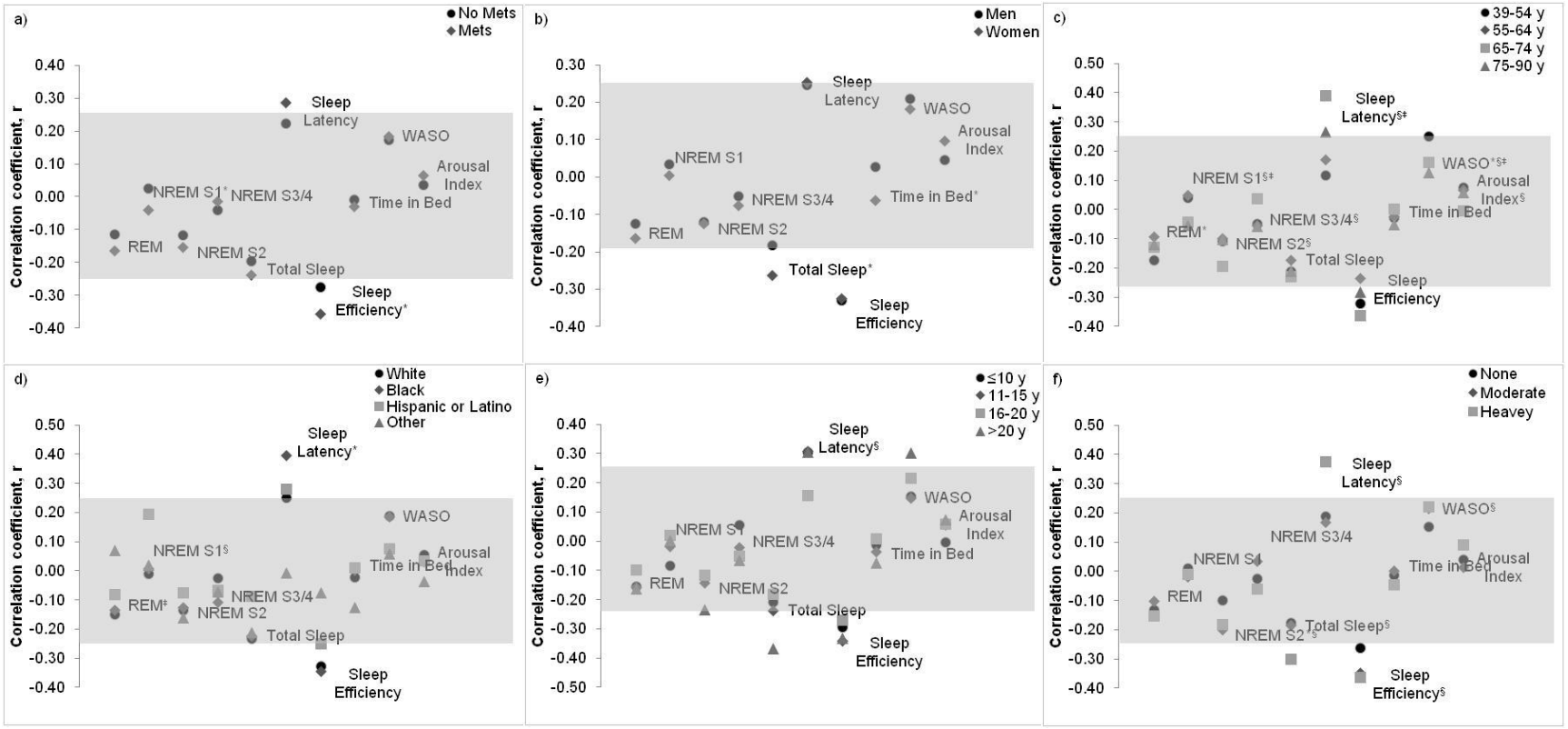


Figure 6.3. Correlation between home-polysomnography-derived sleep measures and the morning survey-based variable time to sleep stratified by MetS (a), sex (b), age (c), ethnicity (d), education (e), and alcohol consumption (f). *p<0.05 for first and second group; §p<0.05 for first and third group; and, ‡p<0.05 for first and fourth group. MetS is metabolic syndrome

Chapter 7 Manuscript 5: Associations between Changes in polysomnography-based total sleep time and sleep efficiency on the risk of developing hypertension, diabetes, dyslipidemia and obesity: a follow-up study

The co-authors of this manuscript are Chris Ardern, Michael Riddell and Alison Macpherson. Thirumagal Kanagasabai and Chris Ardern designed the study. Chris Ardern, Michael Riddell and Alison Macpherson critically revised the manuscript. Thirumagal Kanagasabai performed the statistical analyses and wrote the manuscript.

Abstract

Introduction: Sleep is vital for cardiometabolic health, but research on the changes in sleep duration and efficiency and their associated risk of developing hypertension, diabetes, dyslipidemia, and obesity are sparse. Our objective was to estimate the risk of developing hypertension, diabetes, dyslipidemia and obesity following changes in home-polysomnography (PSG) measured sleep duration and efficiency. **Methods**: To examine this, the Sleep Heart Health Study data cycles 1995-1998 and 2001-2003 were used (≥39 y; N=2,097). Sleep duration and efficiency were assessed with home-polysomnography at baseline and approximately 4 y later. The changes from baseline to follow-up were categorized as decrease (≤5%), increase (≥5%), or no change (change <5%, referent). The usage of medications for hypertension, diabetes, and dyslipidemia, and body mass index (BMI) for obesity were used to define the outcomes. Age, sex, education, alcohol, smoking, marital status and BMI were considered as confounders; BMI was excluded as a confounder in the obesity analysis. **Results**: The number of participants (%) who developed hypertension, diabetes, dyslipidemia, and obesity during the follow-up were 373 (17.79%), 99 (4.72%), 175 (8.35%), and 119 (5.67%), respectively. Those who developed hypertension, diabetes, and dyslipidemia had decreased sleep efficiency; however, an increase in sleep duration increased the relative risk (RR) of developing hypertension (RR (95% CI): 1.29 (1.02–1.64)). Decrease in sleep efficiency increased the RR of developing diabetes and dyslipidemia (1.57 (0.87–2.83); and 1.65 (1.03–2.64), respectively). Neither change in sleep duration nor sleep efficiency increased the risk of developing obesity. **Conclusion**: Sleep efficiency, but not sleep duration, decreases over time, and is related to a higher risk of developing diabetes and dyslipidemia. Sleep

duration increase is associated with a higher risk of developing hypertension. Further research with longer and multiple follow-up periods will help extend our understanding of the relationship between sleep and cardiometabolic health.

Introduction

Even though the importance of sleep for health is well known, societal changes over the last century has forced humans to compromise on our sleep requirements.[12,103] Poorer quality and quantity of sleep are risk factors for cardiometabolic, endocrine, and immune dysfunctions as well as mortality.[20,75,104,105,107,109–112,173] However, most longitudinal studies used baseline self-reported sleep data to estimate the risk of developing cardiometabolic disease.[109–111] Further, many of the large sleep studies have focused on sleep duration and cardiometabolic decline,[38] but emerging evidence suggests sleep quality may be as important for optimizing cardiometabolic health.[25]

Moreover, only limited research exists on the *changes* in sleep habits and their effect cardiometabolic health.[106] Using self-reported sleep data, Ferrie and colleagues[106] found that an increase of ≥2 h in sleep duration between baseline and 5 y follow-up increased the risk of incident diabetes by 50%. Experimental evidence in humans also suggests that *acute changes* in sleep (i.e., sleep deprivation), increases blood pressure, insulin resistance, glucose intolerance, and a preference for calorie-dense foods.[76,149] Indeed, the current knowledge on the longer-term changes in sleep habits and their associated cardiometabolic risks is inadequate. Specifically, the risks of developing hypertension, diabetes, dyslipidemia, and obesity due to changes in sleep habits that were objectively measured in baseline and follow-up are not known.

Therefore, our primary objective is to estimate the relative risk of developing hypertension, diabetes, dyslipidemia, and obesity due to changes in sleep habits over 4-5 y (i.e., approximately 4 y of follow-up). In this regard, we hypothesize that a decrease of 5% or more in sleep duration (i.e., total sleep time) or efficiency between baseline and

the follow-up would increase the relative risk of developing hypertension, diabetes, dyslipidemia, and obesity. Our secondary objectives were to characterize the changes in total sleep time and sleep efficiency over the follow-up, determine the percent conversion from no disease to disease status between the baseline and follow-up, and determine if any differences exist in terms of changes in sleep habits by disease status.

Methods

Sample

To assess our hypothesis, we accessed de-identified data from the Sleep Heart Health Study dataset through the National Sleep Research Resource.[121] The US National Heart, Lung, and Blood Institute of the National Institute of Health funded the Sleep Heart Health Study. The Sleep Heart Health Study dataset contains information on participants from six individual studies: Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, Strong Heart Study, New York Hypertension Cohorts, Tucson Epidemiologic Study of Airways Obstructive Diseases and the Health and Environment Study. The original purpose of this cohort study was to assess the association between sleep and cardiovascular outcomes. The full dataset contains information on participants aged ≥39 y (initial n=6,441), their home-polysomnography (PSG) data and medication history for hypertension, diabetes, dyslipidemia and body mass index (BMI). Data were collected in two follow-ups, approximately 4 y apart: 1995-1998 (n= 5,804) and 2001-2003 (n=4,080). We excluded participants without reliable Rapid Eye Movement/Non-Rapid Eye Movement data (n=85 from the baseline and n=165 from the follow-up), and missing information for hypertension, diabetes, dyslipidemia, and obesity (n=460). Additionally, we excluded those with missing baseline or follow-up total

sleep time and efficiency information (baseline: n=473; follow-up: n=831) for a final analytical sample of n=2,097. Ethics approval was obtained from York University (Toronto, Canada), and was submitted to National Sleep Research Resource to gain access to the dataset.

Sleep and Cardiometabolic health variables

Home-PSG measured total sleep time (original variable name: slp_time), sleep efficiency (slp_eff), and sleep latency (slp_lat) were used in our study. Baseline and follow-up were approximately 4 y apart.[121] We calculated the percent changes from baseline to follow-up for the above sleep habits and categorized them as decrease (≤5%), increase (≥5%), or no change (i.e., change within 5%) for sleep duration (m), sleep efficiency (%), and sleep latency (m). Cardiometabolic health parameters assessed in our study were hypertension, diabetes, dyslipidemia, and obesity. The use of medications indicated for hypertension, diabetes, and dyslipidemia, and BMI for obesity were used to define the outcomes.

Covariates

Baseline age (age_s1), sex (gender), ethnicity (ethnicity and race), education (educat), alcohol (alcoh), cigarette pack-years (cgpkyr), smoking status (smokstat_s1), marital status (mstat), BMI classes (bmi_s1) were used to describe the sample. We categorized age as 39-54, 55-64, 65-74, and 75-90 y. The original race variable was categorized as Whites, Blacks, and Others, and we used the ethnicity variable to further identify the Hispanic or Latino ethic group, and categorized remaining participants as Others. Education categories were based on the number of years in school: ≤10, 11-15, 16-20, and >20 y. Alcohol intake (drinks per day) was categorized as none, moderate,

and heavy using the sex specific cut-offs (i.e. moderate was ≤2 for men and ≤1 for women; heavy was >2 for men and >1 for women) based on the American Dietary Guidelines.[156] Smoking and marital status categorizations were from the original dataset.[121] BMI classes were (kg/m^2): normal weight (<25), overweight (25 to <30), or obese (≥30).

Statistical Analysis

Mean and 95% confidence interval (CI) for the continuous variables, and frequency (n) and frequency % for the categorical variables were determined by sex. T-tests and χ^2 were used, as appropriate, to make comparisons. The sample is also described by the percent changes in total sleep time and sleep efficiency (from baseline to follow-up) as well as disease status. The mean and 95% CI were estimated for the mean difference for the changes in total sleep time and sleep efficiency by disease status. Finally, the crude relative risk (RR) of developing hypertension, diabetes, dyslipidemia, or obesity for those who increased or decreased their total sleep time or sleep efficiency vs. no change (RR=1.00, referent) were determined. The RRs were subsequently adjusted for age, sex, education, alcohol intake, smoking, marital status and BMI in the models predicting the risk of incident hypertension, diabetes, and dyslipidemia. For the model predicting obesity, BMI and marital status were excluded—the former due to collinearity, and the latter due to a lack of sample size. Sleep latency was excluded from the final analyses based on lack of significant findings from the preliminary analyses. All analyses were conducted in SAS v9.3 (Cary, NC, USA) and statistical significance set at an α of 0.05.

Results

The baseline characteristics of the study sample stratified by sex are available in

Table 7.1. In general, the sample is middle-aged, >85% were Whites, and had high school to university level education. Men in the sample smoked more cigarettes and drank more alcohol than the women; they were also more likely to be married than women. A third of the women and a fifth of the men were normal weight. However, more men than women were overweight, and similar proportions of men and women were living with obesity.

Overall, total sleep time increased from baseline to follow-up, and sleep efficiency decreased (**Table 7.2**). Incident diabetes, dyslipidemia, and obesity were rare during the follow-up, i.e., <10%, but hypertension was not (**Table 7.3**). The mean change in total sleep time in the 4 y did not significantly vary between those who developed the disease and those who did not, but the mean change in sleep efficiency was significantly lower amongst those who developed hypertension, diabetes, and dyslipidemia (**Figure 7.1**).

An increase of ≥5% in total sleep time and a decrease of ≥5% in sleep efficiency were associated with significantly higher risk of developing hypertension and dyslipidemia after adjusting for age, sex, education, alcohol intake, smoking, marital status, and BMI, respectively (**Figure 7.2**). In our crude analysis, the RR of developing diabetes was significant (RR (95% CI): 2.21 (1.25, 3.91)) for the decrease in sleep efficiency by ≥5%, but this association attenuated following multivariable adjustment. Sleep latency did not vary across disease status nor did it predict the development of hypertension, diabetes, dyslipidemia or obesity (data not show).

Discussion

In general, total sleep time increased in the follow-up period while sleep efficiency decreased. The development of diabetes, dyslipidemia, and obesity were rare occurrences in the follow-up period, but developing hypertension was common.

Compared to their non-diseased counterparts, those who developed hypertension, diabetes, and dyslipidemia, had significantly decreased sleep efficiency, but not total sleep time. In this study, our primary objective was to estimate the risk of developing hypertension, diabetes, dyslipidemia, and obesity as a result of changes in total sleep time and sleep efficiency in a 4 y follow-up. In this regard, we found that an increase in total sleep time by ≥5% increased the risk of developing hypertension, while a decrease in sleep efficiency by ≥5% increased the risk of developing diabetes and dyslipidemia. These novel findings augment our knowledge on changes in sleep habits and their associated cardiometabolic risk, and thus, warrant discussion.

Hypertension

Most studies used baseline sleep measures to predict incident hypertension risk.[109,112] In our study, we estimated the *change* in sleep over time and estimated the risk of incident hypertension. In this regard, we provide novel evidence that an increase of ≥5% in total sleep time is associated with 29% greater risk of developing hypertension. Indeed, sleep plays a vital role in lowering nocturnal blood pressure through the sympathetic nervous system,[174,175] but this mechanism does not explain our finding in isolation; long sleep duration may be a proxy for poorer sleep quality, less physical activity, and the presence of co-morbidities, such as, depression and obesity, which are all key risk factors for hypertension.[176,177] Therefore, we cannot exclude the possibility that the higher risk of incident hypertension associated with the increased total sleep time may have been due to some of these factors. We adjusted for baseline BMI in our model, and thus, our finding of elevated hypertension risk is independent of obesity. Nevertheless, the causal mechanism between long sleep duration and hypertension risk

remains to be elucidated. One possible mechanism could be the higher systemic inflammation and oxidative stress associated with long sleep duration,[129,178] which stimulates the sympathetic nervous system,[179] and increase the risk of hypertension.[180]

Diabetes

The recent study has found that an increase in self-reported sleep duration by ≥2 h was associated with 50% higher risk of incident diabetes over a 5 y follow-up.[106] However, this study does not align with our null finding for total sleep time, which may be partially due to the fact we used home-PSG to assess sleep. In general, self-reported sleep duration tend to be over reported,[97] and most previous studies used baseline self-reported sleep to estimate the risk of incident diabetes.[16,111,181] Our finding that the decrease in sleep efficiency increased the risk of incident diabetes provides new information on the role of longer-term changes in sleep efficiency and diabetes risk. This finding awaits confirmation in other prospective settings.

Indeed, sleep loss is associated with elevated levels of circulating glucose through decreased non-insulin dependent utilization of glucose in the brain, which results in insulin resistance, and thus diabetes risk.[149] Sleep loss also increases appetite through the deregulating of leptin and ghrelin pathways, which contribute to weight gain and obesity.[149] Therefore, changes in sleep behaviours might be important predictors of diabetes risk, and both aging and our society are contributing to decreased sleep.[12,74,97,182]

Dyslipidemia

Our study has found that decreased sleep efficiency was associated with 65% increased risk for incident dyslipidemia within the 4 y follow-up. The obvious explanation

for the relationship between decreased sleep and incident dyslipidemia is the affect of sleep deprivation on dietary intake of fats.[27] Indeed, those who are sleep deprived tend to have a preference for high fat and high carbohydrate foods,[76] which promotes weight gain and obesity.[183] An alternative explanation for our finding is that the use of statins induces sleep disturbances[184] and sleep deprivation.[185] The lipophilic properties of the drug may enable it to penetrate the blood-brain barrier and inhibiting prostaglandin D2 synthase in the central nervous system, and thus interfere with sleep.[186,187] However, further research is needed to test this mechanistic hypothesis.

Obesity

Compared to the US population, the men in our sample were more likely to be overweight or living with obesity, i.e., 79% of the men were either overweight or living with obesity at baseline.[188] However, neither change in home-PSG measured total sleep time nor sleep efficiency increased the risk of developing obesity in the 4 y follow-up. A possible explanation for this may be due to the short follow-up period in our study, where just over 5% of the sample developed obesity. Our null finding is unlikely due to adjusting for covariates because our crude model as well as the mean differences for total sleep time and sleep efficiency between normal weight and obese sample were not significant. Indeed, other research support the relationship between sleep deprivation and obesity,[74,189–192] and thus, longer prospective studies using multiple follow-ups of sleep are needed.

Limitations

A major limitation of our study is that we were unable to account for the other factors that influence both sleep and cardiometabolic health, such as physical activity and

diet, because they were not available. However, an advantage of our study is that the dataset contained home-PSG measured sleep parameters for both the baseline and the follow-up. The home-PSG sleep measures were assessment for 1 day at baseline and 1 day approximately 4 y later, and thus, it only gives a snapshot of participants sleep habits, which may not be reflective of their usual sleep. Further, the lab-PSG is considered the gold standard to assess sleep objectively, while we used home-PSG derived data, but research suggests the two methodologies vary only minimally.[172] Finally, because we used medication use to define incident hypertension, diabetes, and dyslipidemia, our estimates for these diseases are likely conservative, i.e., we assumed the presence of these disease were being treated by medications, and thus, we cannot account for undiagnosed cases. However according to the National Health and Nutrition Examination Survey data, this may account up to 8% of the US adults for hypertension and hypercholesterolemia, and 3% for diabetes.[193] Further, nearly a quarter of the population with hypertension are not taking medications for it.[194]

Conclusion

Our study found that an increase in sleep duration is associated with higher risk of developing hypertension, while a decrease in sleep efficiency is associated with higher risk of developing diabetes and dyslipidemia that requires pharmaceutical treatments. Further research should assess the direction of sleep habit change over longer timeframe to understand the casual relationship between changes in sleep habits and cardiometabolic health risks.

Table 7.1. Baseline characteristics of the study participants

		Men (n=978)	Women (n=1,119)	p value
Age (mean (95% CI))		62.2 (61.6, 62.9)	62.1 (61.4, 62.7)	NS
Age category (n (%))				
	39-54 y	230 (23.5)	283 (25.3)	NS
	55-64 y	330 (33.7)	356 (31.8)	
	65-74 y	289 (29.6)	319 (28.5)	
	75-90 y	129 (13.2)	161 (14.4)	
Ethnicity				
	White	871 (89.1)	972 (86.9)	NS
	Black	52 (5.3)	77 (6.9)	
	Hispanic or Latino	37 (3.8)	56 (5)	
	Other	18 (1.8)	14 (1.3)	
Education				
	≤10 y	57 (6.4)	70 (7)	<0.05
	11-15 y	433 (48.9)	590 (58.9)	
	16-20 y	330 (37.3)	311 (31)	
	>20 y	65 (7.3)	31 (3.1)	
Alcohol				
	None	400 (43.6)	647 (61.3)	<0.05
	Moderate	162 (17.7)	153 (14.5)	
	Heavy	356 (38.8)	256 (24.2)	
Cigarette pack-years (mean (95% CI))		16.2 (14.9, 17.6)	8.9 (7.9, 9.9)	<0.05
Smoking status (n (%))				
	Never	346 (35.5)	648 (58.1)	<0.05
	Current	95 (9.7)	85 (7.6)	
	Former	534 (54.8)	383 (34.3)	
Marital Status				
	Married	874 (91.2)	790 (72.3)	<0.05
	Widowed	19 (2)	153 (14)	
	Divorced/Separated	45 (4.7)	115 (10.5)	
	Never Married	20 (2.1)	35 (3.2)	
Body Mass Index				
	Normal Weight	204 (20.9)	371 (33.2)	<0.05
	Overweight	476 (48.7)	418 (37.4)	
	Obese	298 (30.5)	330 (29.5)	

Alcohol cut-offs are sex-specific (heavy for men >2 drinks per day, and for women >1 drink per day).

Table 7.2. Percent changes in total sleep time and sleep efficiency from baseline to follow-up.

	Percent Changes		
	≤ 5%	**<5%**	**≥ 5%**
Total Sleep Time (m)	597 (35.54)	398 (23.69)	685 (40.77)
Sleep Efficiency (%)	650 (45.49)	451 (31.56)	328 (22.95)

Table 7.3. Incident hypertension, diabetes, dyslipidemia, and obesity between baseline and follow-up

	No disease	Disease
Hypertension (n (%))	764 (36.43)	373 (17.79)
Diabetes	1902 (90.7)	99 (4.72)
Dyslipidemia	929 (44.3)	175 (8.35)
Obesity vs. Normal Weight	568 (27.09)	119 (5.67)

Figure 7.1

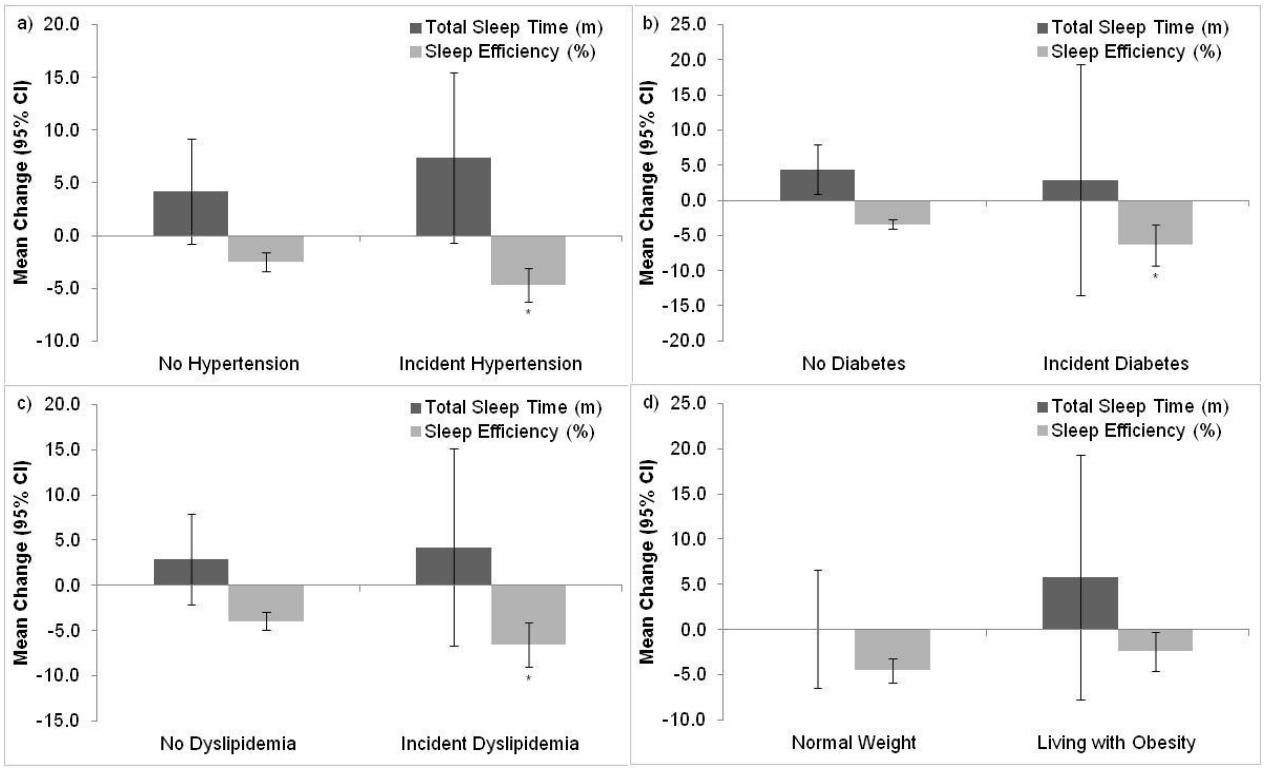


Figure 7.1. The mean difference for the changes between baseline and follow-up of total sleep duration and sleep efficiency in those with and without hypertension (a), diabetes (b), dyslipidemia (c), and obesity (d).

*$p<0.05$ for no disease vs. disease.

Figure 7.2

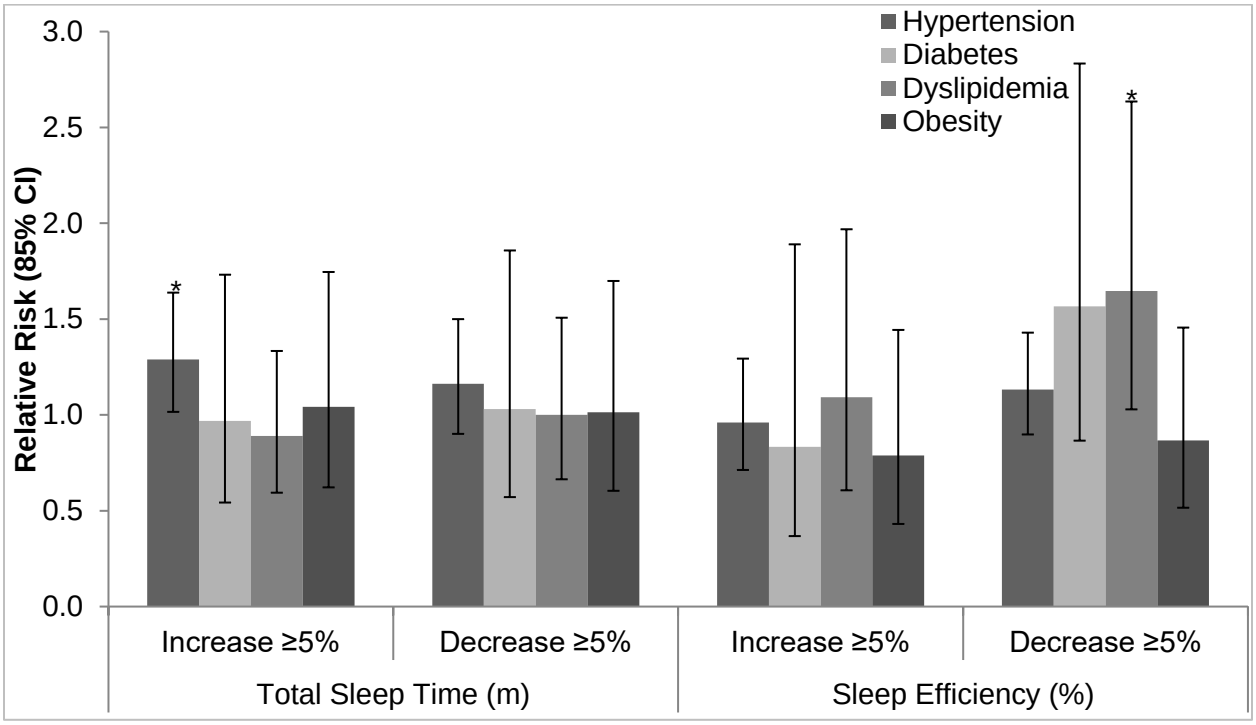


Figure 7.2. Adjusted relative risk of developing hypertension, diabetes, dyslipidemia and obesity between baseline and follow-up.

Hypertension, diabetes, and dyslipidemia were adjusted for age, sex, education, alcohol intake, smoking, marital status, and BMI. Obesity was adjusted for age, sex, education, alcohol intake and smoking. Referents were no hypertension, diabetes, dyslipidemia or normal weight, and total sleep time or sleep efficiency change of <5%. *p<0.05.

Chapter 8 General Discussion

Despite the well-known relationship between sleep and cardiometabolic health, sleep deprivation is a common feature of modern society.[195] Since sleep quality and duration are necessary for health; they can be considered as two sides of the same coin. However, it is much easier to obtain sleep duration data from participants than sleep quality data, especially from a population perspective.[170] Therefore, much of the known research on sleep and cardiometabolic health has focused on sleep duration.[29,38,196] Further, the limited research on sleep quality has produced mixed results because there is a lack of consensus on the definition of sleep quality.[170] This, however, is a challenge that may never be resolved because sleep is a behaviour that has changed over time in human history. For instance, before the 17th century, humans slept in two chunks of 4 h because the nighttime was reserved for creatures of the night, and candles were expensive.[197] Modernization, work/life pressures, social jet lag, and the boom in technology are some reasons that have forced the average adults to sleep below 7 hours per night in the recent year.[12,17] This parallels modern society's higher rates of non-communicable chronic diseases, particularly cardiometabolic diseases.[114,189,198]

This dissertation augments current knowledge about the relationship between sleep and cardiometabolic health in several ways. The first part of the dissertation provides evidence for the contributing role of physical activity and dietary factors to the causal relationship between sleep and cardiometabolic health. These are summarized in **Table 8.1** for sleep duration and **Table 8.2** for sleep quality. Additional details on the contributions of dietary factors to the relationship between sleep and fasting insulin concentration are available in **Figure 9.1**. The main objective of the additional analysis

was to estimate the contributions of inflammation, oxidative stress, and antioxidants to the causal relationship between sleep and fasting insulin level. Therefore, the main conclusions from this dissertation work suggest that physical activity and dietary factors have some, but not complete influence on WC, BP, and fasting insulin concentration. Indeed, this aligns with most observational studies,[25,31,38,114] but this was the first time the mediating effect of these factors on the causal relationship between sleep parameters and cardiometabolic health was explored.

Inflammation and Oxidative Stress

Our results suggest inflammation and oxidative stress can largely explain the relationship between sleep and cardiometabolic health, particularly when the outcome is WC, SBP, or fasting insulin concentration. In populations with sleep disorders, the prevalence of obesity is high; and, both sleep quality and obesity have been independently linked to increased inflammation and decreased antioxidants.[78,189,199] Indeed, insulin resistance is a common feature associated with sleep deprivation, which can affect the non-insulin dependent utilization of glucose in the brain resulting in chronically elevated blood glucose.[149] This causes the pancreas to increase insulin output and over time contributes to the development of insulin resistance.[200] Future studies in this area should also assess alternative markers of glycemic control, such as the homeostatic model assessment (HOMA), which uses fasting glucose and insulin or C-peptide concentrations to assess pancreatic β-cell function and insulin resistance.[149,201,202]

Further, GGT is a diagnostic tool for alcoholism and fatty liver, conditions associated with elevated waist circumference, blood pressure, and dyslipidemia.[47,52] We

used GGT as a biomarker of oxidative stress,[47,54] and demonstrated that oxidative stress lies on the causal pathway of the relationship between sleep duration and obesity, blood pressure, and fasting insulin level.[203,204] Hence, GGT may be a useful clinical measure of oxidative stress,[47] and strategies to reduce oxidative stress and chronic inflammation would be effective against cardiometabolic dysfunction.[46] Indeed, oxidative stress and inflammation are commonly associated with several chronic diseases, including diabetes, and cardiovascular disease.[9,46,69,105] Therefore, further research using additional biomarkers of oxidative stress and inflammation, such as superoxide dismutase, glutathione peroxidase, catalase, interleukin-6, and tumour necrosis factor-α, may further our understanding of the causal role of inflammation and oxidative stress in sleep and cardiometabolic outcomes.[55,178,199,205–207] Understanding the mediatory role of these factors in humans may help identify inflammation and oxidative stress pathways that may be targeted by therapeutics.[208]

Carotenoids

Adequate serum carotenoids level is a marker of a healthy diet rich in vegetables and fruits.[209] Indeed, lower serum and dietary β-carotenes levels in those with MetS have been found,[8,57,209] but dietary and serum β-carotene level do not always correlate strongly.[210] Notably, this dissertation was the first work to evaluate the contributing role of carotenoids in the relationship between sleep duration and WC, SBP, and fasting insulin. The antioxidant property of carotenoids may reduce systemic inflammation and thus influence the above relationships.[8] People who consume a healthy diet rich in vegetables and fruits also tend to get adequate sleep.[70] Therefore, carotenoids may be important for cardiometabolic health, but longitudinal studies are needed to confirm and

further extend our understanding of their mediating roles on sleep and cardiometabolic health.

Uric Acid

This dissertation work was the first to evaluate the contributing effect of uric acid on the sleep—cardiometabolic health relationship. In this regard, we found that uric acid was a great mediator of the sleep—WC,—SBP, and —fasting insulin relationships. Other human studies have found an association between uric acid and metabolic dysfunction.[58,59,62–66,211,212] A well-known feature of the modern high-fructose diet is elevated serum uric acid levels.[67] In rats, a high-fructose diet causes uric acid levels to increase and contribute to the development of MetS.[61] Indeed, uric acid may play key roles in the pathogenesis of high fructose diet-induced MetS by reducing acetylcholine-mediated arterial dilation and inducing insulin resistance by reducing the bioavailability of endothelial nitric oxide.[61,67]

Vitamin C

The finding that vitamin C contributes to the casual relationships between sleep and WC, BP and fasting insulin are novel. Vitamin C, rich in fruits and vegetables, is a potent antioxidant, and it is found to be decreased in those with cardiometabolic dysfunction.[8,57,80,213–215] It is also inversely related to BMI, percent body fat, and waist circumference[213] and blood pressure.[80,214] In fact, vitamin C supplements improved endothelial function in obstructive sleep apnea patients,[80] and lowered systolic blood pressure in elderly.[216] The exact mechanism is not known, but the antioxidant protection vitamin C provides against oxidative stress may partially be responsible.[217]

Vitamin D

Finally, vitamin D contributed to the relationship between sleep duration and WC, SBP, and fasting insulin. Others have found an association between vitamin D and cardiometabolic dysfunction,[56,218–220] while some research suggests vitamin D supplementation improves sleep.[221,222] Further, visceral adipose tissue is strongly associated with vitamin D level (β:−2.34, p <0.0001) following adjustments for sex, season, systolic blood pressure, physical activity, vitamin d intake, and insulin.[56] Some evidence also suggests that a vitamin D level of >80nM protects against age-related systolic blood pressure increase.[218] Additionally, early supplementation with vitamin D has been implicated in reduced type 1 diabetes risk, as vitamin D has immune-modulating and antioxidant properties.[223,224] Another mechanism that may explain the relationship between vitamin D and insulin resistance is the increased insulin receptor gene transcription.[225]

Beyond the findings from this dissertation, additional epidemiologic and experimental studies are needed to confirm and extend our understanding of the factors that influence the relationship between sleep and cardiometabolic health. This includes the need to repeat the present analysis using other population datasets to confirm our findings. Additionally, diet- vs. supplemental-based experimental studies in humans may help evaluate the effect of micronutrients to the relationship between sleep and cardiometabolic health. From a practical standpoint, implementing policy changes that promote micronutrient-rich diets (i.e., reducing the costs of fresh fruits and vegetables, and increasing the costs of processed foods) and evaluating the effectiveness of those policy changes, is needed to better understand the relevancy of these strategies [226–229]

Physical Activity

Similarly, we evaluated the contributions of accelerometer-based physical activity counts to the relationship between sleep and cardiometabolic health. Most previous work has considered physical activity as a confounding variable to the sleep and cardiometabolic health relationships.[16,89,118,136] This dissertation work provides evidence that moderate intensity and lifestyle activity levels explain the causal relationships of sleep–WC, sleep–BP, and sleep–fasting insulin concentration. Specifically, the contributions of non-exercise activity thermogenesis from lifestyle activity level suggests that it may contribute to the overall cardiometabolic health of adults, supporting previous research in this area.[82,138] Indeed, the relationship between physical activity and nocturnal BP dipping through the suppression of the sympathetic nervous system is known.[89] Further, the beneficial effect of physical activity in protecting against insulin resistance is well known,[149,150] but this work is the first to quantify the actual contributions of physical activity to the casual relationship between sleep and fasting insulin levels. However, additional studies in other populations are needed to confirm the accuracy of our estimates. For instance, the mediatory effect of physical activity may be altered in developing countries where the majority of the population engages in active transportation, and their sleep habits also differ from the US population.[230–232] Further, the relationships investigated this dissertation may be confounded or moderated by other factors (e.g. level of physical fitness, sex, BMI, and ethnicity, etc.), meaning that future studies should include these factors to produce more accurate estimates.[1,189,190,233–235]

Objective vs. Subjective Sleep

Consistent with previous work, we found modest-to-moderate correlation between PSG and self-reported sleep measures in those with MetS.[95,97,100–102] However, the

novelty of our findings lies in our subpopulation analyses. We found that women, for instance, are more perceptive of their sleep habits than men, but research suggests they tend to over-report sleep problems.[95] Age, socio-economic status, and co-morbidities are other factors influencing one's perception of sleep.[97,159] Therefore, further research in this area is needed to understand better the relationship between objective vs. subjective measures of sleep variables. Additional research using alternative objective data collection tools (e.g., accelerometer and smartphone apps) and statistical methodologies (e.g., Bland-Altman analysis, Cronbach's alpha, and kappa statistics) are also needed to confirm and better understand the relationship between objective and perceived sleep measures.[236–241] There is also an urgent need to develop a consistent definition of sleep quality for research and clinical purposes.[120] Identifying the variations in subgroups, such as MetS vs no MetS, men vs women, older adults, and obesity, as has be done, is also an essential step toward making recommendations on population-specific sleep requirements.[120,165,190,192,242,243]

Sleep, Obesity and Metabolic Syndrome

We found that having MetS or living with obesity reduced objective total sleep, which aligns with previous literature on sleep duration with MetS,[38] and obesity.[75] This work is significant in that the difference in sleep duration was found to be <10 minutes after adjusting for age, sex, obesity or MetS. Moreover, when the reverse relationship between sleep and MetS was evaluated, the effect of the objectively derived sleep variables had little effect on the odds of having MetS, independent of body weight, age, and sex. However, nearly a half of the population living with obesity has diagnosed sleep disorders, which may be a cause or consequence of obesity.[244,245] To date, the

directionality of the relationship remains unknown, but acute sleep curtailment studies suggest higher caloric intake and lower physical activity level are common amongst sleep deprived individuals.[246] Over time, chronic sleep deprivation and lower sleep quality likely lead to weight gain through changes in appetite regulation.[191,247] Therefore, clinical guidelines and policies aimed at preventing, managing and treating obesity through promoting in sleep hygiene may help minimize the burden of obesity related co-morbidities, such as cardiovascular disease.

Change in Sleep Habits and Cardiometabolic Risk

The final part of this dissertation explored the relationship between objectively measured change in sleep habits and their associated risk of developing cardiometabolic diseases. Previously, one study has evaluated the effect of changes in sleep habits and their effect cardiometabolic health and found that an increase of ≥2 h in self-reported sleep duration between baseline and 5 y follow-up increased the risk of incident diabetes by 50%.[106] Other studies using baseline self-reported sleep only has also found that sleep deprivation increases the risks of developing diabetes, hypertension, cardiovascular events, and obesity.[75,107–112] This dissertation augments current knowledge by providing evidence that a modest (≥5%) 4 y increase in sleep duration increases the risk of developing hypertension, while a ≥5% decrease in sleep efficiency increases the risk of developing diabetes and dyslipidemia. Our estimates are likely conservative in that these outcomes were defined by i) a self-report of physician-diagnosis of diabetes, hypertension and high cholesterol, or ii) use of medication to treat one or more of these conditions. Studies using clinical or laboratory data are therefore needed to confirm our findings and to determine the causes for changes in sleep habits, in order to develop therapeutic

targets or policy changes to offset reductions in sleep habits over time.[248] For instance, if blue light exposure is identified as a culprit of reduced sleep, policies may be developed for the manufacturers of electronic devices to automate the blocking of sleep inhibiting blue light from electronic devices between 9 pm and 6 am, a few hours before the time of typical sleep onset.[249–252] This will help ensure a consistent bedtime, another factor that is important for cardiometabolic health.[253]

A possible explanation for the higher incidence of hypertension amongst the longer sleep duration may indicate poor sleep quality, less physical activity, or the presence of co-morbidities.[176,177] The latter findings for sleep efficiency are novel, as a change in objective sleep efficiency has not been previously explored in this context. Future research is however needed to determine whether changes in sleep habits affects the nocturnal BP dipping, subtly increases the sympathetic nervous system activity, or acts through other mechanisms, and thus, increases hypertension.[254] Several possible mechanisms may explain the higher diabetes and dyslipidemia risks. Change in sleep efficiency, for instance, may result in elevated glucose, which over time induces insulin resistance, and thus diabetes.[149] Further, sleep loss alters the appetite-regulating hormones, leptin and ghrelin, which in turn contributes to weight gain and obesity.[182,190] Sleep loss is also associated with increased preference for the intake of foods rich in fats and carbohydrates, which can induce obesity and alter serum cholesterols.[76] However, the effect of modest or gradual sleep loss and their influence on appetite regulations warrants further study, as it may help explain several present chronic disease epidemics including obesity, diabetes, and cardiovascular disease.[255,256]

Conceptual framework

Indeed, this work aligns with the conceptual framework for the relationship between sleep and cardiometabolic health, which was originally developed by Buxton *et al*.'s[28]. According to this framework, socio-cultural and environmental factors (i.e., individual and community level factors) influence sleep (ie., decrease sleep duration and quality), which induces proximal changes by interfering with energy homeostasis (i.e., decreased physical activity/intensity, increased intake of processed, energy-dense, nutrient-deficient foods), which over time could speed up the progression of clinical changes.[28] Specifically, evidence from this work supports that physical activity and dietary habits lie on the causal pathway of the relationship between sleep and cardiometabolic health in the first three studies. Although we explored this relationship in a cross-sectional setting, we found evidence that the pathways may be more immediate than Buxton *et al*.'s[28] conceptual framework suggests. Particularly in the fifth study, we found that changes in sleep habits in a relatively short follow-up of 4 y increased the risk of developing hypertension, diabetes and dyslipidemia after adjusting for confounders. Therefore, this dissertation provides insight into the mechanistic relationship of longer-term sleep deprivation on chronic disease risk within Buxton *et al*.[28] framework, and it augments the framework by providing evidence for the relationship between sleep quality and cardiometabolic risk. This work, however, did not explore the influence of socio-cultural and environmental factors on sleep, and this remains an important area that warrants further study. Studies with the NHANES dataset can be performed to assess the influence of socio-cultural/economic and environmental factors to further test this conceptual framework.[116] Doing such analyeses may provide insights that can be used to develop and implement strategies to improving the health of specific subgroups.

Additionally, this dissertation found that the mediatory effect of diet and physical activity on the relationship between sleep and cardiometabolic health was stronger in women than men. Sex, BMI, age, ethnicity, income, education, smoking and alcohol intake may therefore be significant modifiers of the overall relationship, and future research in this area is needed to more fully develop the conceptual framework used in this dissertation.[17,22,167,190,257] This framework should also be tested with longitudinal datasets from both developed and developing countries, so as to better understand the broader generalizability of the framework.

Limitations

A major limitation of the first four manuscripts is the use of cross-sectional data, which has not been traditionally used to make a casual inference, first three manuscripts, since the temporal relationship—whether the exposure preceded the outcome—cannot be determined. Another limitation of our studies is the extensive use of self-reported data, which are susceptible to the healthy responder and recall biases. However, the NHANES is a rich source of data with dietary, physical activity, sleep and cardiometabolic parameters, and an alternative longitudinal dataset is not presently available for any representative adult population.[116,258] Although the SHHS dataset contains objective sleep and self-reported or measured anthropometric and cardiometabolic disease markers, it lacks physical activity and dietary information.[121] Although the first part of the dissertation uses the NHANES includes serum biomarkers and accelerometer-derived activity as proxies for dietary and physical activity habits (to minimize recall bias)[141,258,259], participation in NHANES is voluntary, and thus, the findings may be biased toward the null since healthier participants tend to volunteer for scientific studies.[116] The SHHS also

used a non-probably sample selection process, and thus, the generalizability of this work to the US adult population may be reduced.[260] The first three studies were also unable to evaluate the effect of confounders and potential modifiers of the relationship between sleep, diet, physical activity and cardiometabolic health (e.g., obesity, age, and sex).[142,261] As a result, this work is baised toward the "forward" direction of the relationship in the conceptual framework, while some evidence for a bi-directional association between the factors included in the model exists.[262–264] Future work should consider the "reverse" direction of the conceptual framework used in this dissertatoin (e.g. increase sleep efficiency and its effect on cardiometabolic health). Finally, we used data that are more than a decade old, and therefore, it is unclear whether these findings apply to the contemporary population. Specifically, the recent surge in smartphone use may have altered sleep habits amongst the contemporary population, and thus, the relationship between sleep and cardiometabolic risk may have also altered.[265,266] Future studies with longitudinal, time-relevant, and objectively measured data are needed to further extend our understanding of the relationships studied in this work.

Conclusion

In conclusion, this work demonstrates that the relationship between sleep and cardiometabolic health can be explained partially by physical activity and dietary behaviours. Indeed, a holistic approach that includes sleep, physical activity and diet is needed to improve the cardiometabolic health profile of free-living adults. Guidelines and policies should be developed to target the three areas simultaneously, such as the guidelines for sleep, physical activity, and sedentary time in development for children.[115] One remaining factor that may influence the above relationship is social engagement,

which serves a vital part in sleep, diet, and physical activity behaviours.[267,268] Therefore, additional research in this area may provide insight into the role of social influence as a focus of intersection to this work.

Table 8.1. Summary of the mediation effect for sleep duration

		Cardiometabolic Health						
Mediator	**MetS**	**# of Mets**	**WC**	**SBP**	**DBP**	**TG**	**HDL**	**FPG**	**Insulin**
C-reactive Protein (nM)									
γ-Glutamyl transferase (U/L)			1	1					2
Bilirubin (μM)									
Carotenoids (μM)			2	1					2
Uric Acid (μM)			2	2					2
Vitamin A (μM)									
Vitamin C (μM)			2		1				2
Vitamin D (nM)			2	1					
Vitamin E (μM)									
Lifestyle Moderate Activity (min/d)			2	2	1				2
Light Activity (min/d)			1						
Moderate Activity (min/d)									
Moderate and Vigorous Activity (min/d)									
Vigorous Activity (min/d)									
Sedentary Activity (min/d)									

Significant mediation effect; 1=moderate (≥0.09) and 2=large effect (≥0.25). MetS is metabolic syndrome. # of MetS is number of MetS components. WC is waist circumference. SBP is systolic blood pressure. DBP is diastolic blood pressure. TG is triglycerides. FPG is fasting plasma glucose. HDL is high-density lipoprotein cholesterol. Insulin is fasting insulin concentration. Activity thresholds (counts per minute) were sedentary activity (0–99), light intensity (100–759), lifestyle activity (760–2019), moderate intensity (2020–5996), and vigorous intensity (≥5999).

Table 8.2. Summary of the mediation effect for sleep quality

			Cardiometabolic Health						
Mediator	**MetS**	**# of Mets**	**WC**	**SBP**	**DBP**	**TG**	**HDL**	**FPG**	**Insulin**
C-reactive Protein (nM)			**1**						**2**
γ-Glutamyl transferase (U/L)									
Bilirubin (µM)									**2**
Carotenoids (µM)									
Uric Acid (µM)									
Vitamin A (µM)				**1**					
Vitamin C (µM)			**1**						**2**
Vitamin D (nM)									
Vitamin E (µM)									
Lifestyle Moderate Activity (min/d)			**1**	**1**	**1**				**2**
Light Activity (min/d)									
Moderate Activity (min/d)			**1**	**1**					**2**
Moderate and Vigorous Activity (min/d)			**1**	**1**					
Vigorous Activity (min/d)									
Sedentary Activity (min/d)									

Significant mediation effect; 1=moderate (≥0.09) and 2=large effect (≥0.25). MetS is metabolic syndrome. # of MetS is number of MetS components. WC is waist circumference. SBP is systolic blood pressure. DBP is diastolic blood pressure. TG is triglycerides. FPG is fasting plasma glucose. HDL is high-density lipoprotein cholesterol. Insulin is fasting insulin concentration. Activity thresholds (counts per minute) were sedentary activity (0–99), light intensity (100–759), lifestyle activity (760–2019), moderate intensity (2020–5996), and vigorous intensity (≥5999).

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Chapter 9 Appendices

Appendix A: Manuscript 1

Citation: Kanagasabai, Thirumagal, and Chris I. Ardern. “Contribution of Inflammation, Oxidative Stress, and Antioxidants to the Relationship between Sleep Duration and Cardiometabolic Health.” *Sleep* 38, no. 12 (2015): 1905–12.

Appendix B: Manuscript 2

Citation: Kanagasabai, Thirumagal, and Chris I. Ardern. “Inflammation, Oxidative Stress, and Antioxidants Contribute to Selected Sleep Quality and Cardiometabolic Health Relationships: A Cross-Sectional Study.” *Mediators of Inflammation* 2015 (2015): 824589.

Appendix C: Additional Analysis for the Fasting Insulin Level Outcome

Figure 9.1

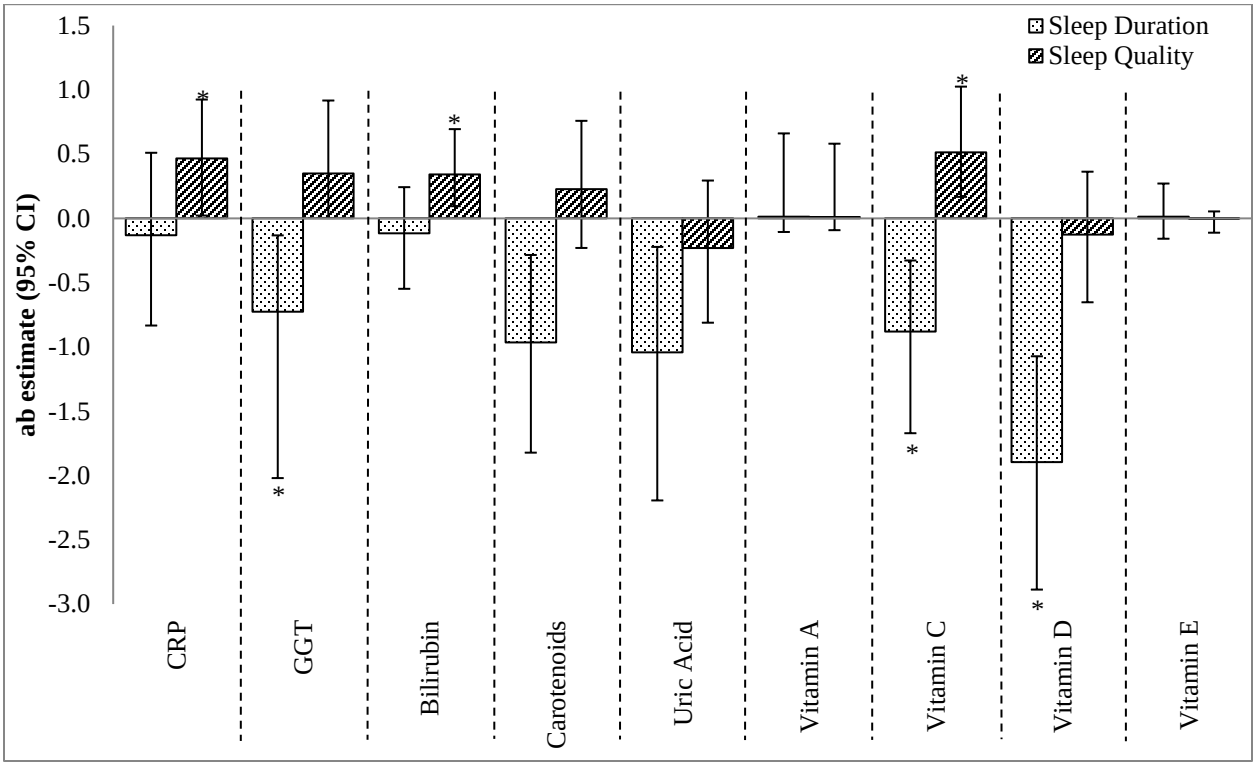

Figure 9.1. The contributions of inflammation, oxidative stress, and antioxidants to the sleep–fasting insulin level relationship.

ab estimate is amount of mediation or contribution by the mediatory variable; CI, confidence interval. *p<0.05, 95% CI are bias-corrected, bootstrapped values.

Appendix D: A Brief Description of the National Health and Nutritional Examination Survey (NHANES) and the Sleep Hearth Health Study Datasets

NHANES

The National Health and Nutrition Examination Survey (NHANES) is a series of cross-sectional studies designed to assess the health and nutritional status of adults and children in the United States. It collects data from personal interviews, physical examinations, and laboratory analyses biannually in a nationally representative sample of approximately 10,000 participants. Laboratory data are obtained by blood and urine samples collected from survey participants at NHANES Mobile Examination Centers within approximately 2 weeks of the interview. Health status is assessed by physical examination at the Examination Centers. Demographic and other survey data regarding health status, nutrition, and health-related behaviors are collected by personal interviews.[116] Further details of the protocols and sample processing methods are available on the NHANES's website.[258]

NHANES uses a complex, multistage, probability sampling method to select participants that are representative of the US civilian, non-institutionalized population. However, NHANES uses randomly samples households (stage 3) and individuals (stage 4).[269] Stage 1 are counties, and stage 2 are segments within the countries. Selection at stages 1 and 2 levels are based on the "probability proportional to a measure of size".[269] In some instances, certain subgroups are oversampled to better estimate the health risks in these groups.[269] Finally, a sample weight is assigned to each participant to represent the number of people in the population based on the census data.[269]

Sleep Heart Health Study

The Sleep Heart Health Study dataset was obtained from the National Sleep Research Resource portal.[121] This is a multicenter (6 cohorts), longitudinal study that began in 1994, and completed in 2011. The 6 cohorts were: Atherosclerosis Risk in Communities Study (n=1,750); Cardiovascular Health Study (n=1,350); Framingham Heart Study (n=1,000); Strong Heart Study (n=600); New York Hypertension Cohorts (n=1,000); and, Tucson Epidemiologic Study of Airways Obstructive Diseases and the Health and Environment Study (n=900). The Sleep Heart Health Stud's main purpose was to determine if sleep-disordered breathing increased risk of developing cardiovascular disease and all-cause mortality.[260] A non-probability sampling method was used to select participants who were ≥40 y with had no history of treatment for sleep apnea, tracheostomy, or current home oxygen therapy.

The initial home-PSG was done between 1995 and 1998, and the follow-up home-PSG approximately 4 y later (2001 to 2003). In total, 6,441 participants were enrolled in the first cycle, and 3,295 of the participants completed the follow-up cycle home-PSG protocol. Data were collected for both baseline and follow-up via home visits by trained personnel who were certified to set up the sleep monitor and obtain vital measurements, and collect data from the interviews, as well as review the completeness data.[121] A technician also returned to the participant's home the following morning to collect the sleep monitor and self-administered survey data. These data were checked by sleep technicians for completeness and quality, and the PSG data were sent to the Reading Center for processing.[121]

Appendix E: Sample Sizes needed to have 80% Power

To detect a moderate mediation effect of ≥0.09 with 80% power, 105 participants were required in each sleep category for manuscripts 1 and 2.[142] Therefore, we had sufficient power in these studies. For manuscript 3 and the additional analysis, which uses the bootstrap method, a similar sample size has 80% power (i.e., n=100) to detect a moderate mediation effect.[270] Therefore, we were slightly underpowered for our analyses for sleep duration for manuscript 3 because the very short and long sleep durations were below 100. However, we used 5000 iterations instead of the 1000 iterations used by Lockwood & MacKinnon[270] in their simulation, which gives a more accurate estimation of the errors within the model. Further, the overall patterns of our analyses are similar for both sleep duration and quality, and we had sufficient power for our sleep quality analyses.

For manuscript 4, a sample size of 97 participants was needed to detect a modest correlation of ≥0.25 with 80% power. For the multiple regression analyses in this manuscript, which had 4 predictors, a sample size of 45 was required to detect 30% higher odds of MetS. For the multiple linear regression model with 4 predictors, a sample size of 1,188 was required to detect a difference as small as 0.01.[271] Therefore, this study was adequately powered.

For manuscript 5, a sample size of 61 participants per group was needed to detect a 30% higher risk in the final model that included 9 predictors.[271] Therefore, this study was sufficiently powered.

Appendix F: Mediation Analyses, Sample SAS Code, Outputs, and Explanation

Mediation Analysis

Mediation analysis is a series of regression analyses that help explain the underlying relationship between an exposure and an outcome through a third, mediatory variable. Path a is the relationship between exposure and mediator. Path b is the relationship between the mediator and outcome controlling for the effect of the exposure. Path c is the relationship between exposure and outcome. Path c' is relationship between exposure and outcome controlling for the effect of the mediator.[142] These paths are illustrated in **Figure 9.2**. In a mediation model with the same cases in all paths and no latent variables, the products of paths ab and c-c' are mathematically equivalent. The indirect effect (*ab)* estimate is the amount of contribution a mediator provides to the relationship between an exposure and an outcome.[142]

total effect (c) = direct effect (c') + indirect effect (ab)

indirect effect (ab) = total effect (c) - direct effect (c')

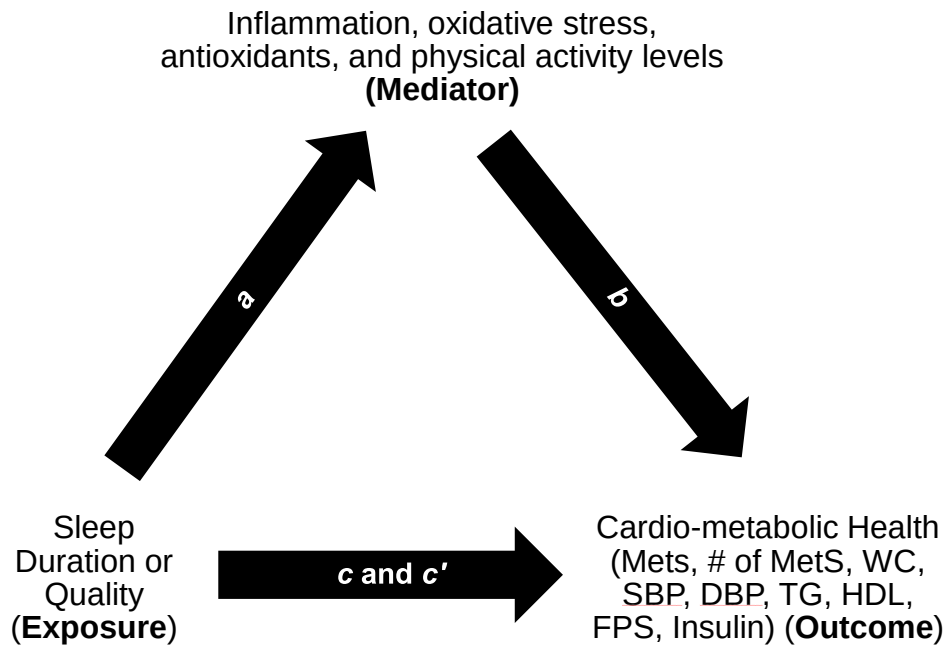

Figure 9.2. Multiple regression method of the indirect mediation model.

Path a indicates the path from sleep quality (exposure) to mediator (i.e., inflammation, oxidative stress, and antioxidant. Path b indicates the path from mediator to outcome (i.e., metabolic syndrome (MetS), number of MetS components, and individual MetS components) controlling for the mediator. Path c indicates the path from exposure to outcome. Path c' indicates the path from exposure to outcome controlling for the mediator. The paths of this figure are from Kenny.[142]

Sample SAS Code

```
*Path a;
PROC REG;
MODEL CRPSI = sleepqualitycat;
RUN;

*Paths b and c';
PROC REG;
MODEL INSULINPMOL = CRPSI sleepqualitycat;
RUN;

*Path c;
PROC REG;
MODEL INSULINPMOL = sleepqualitycat;
RUN;
```

Sample Output for the Individual Paths

Path a output:

Parameter Estimates					
Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	1	0.03995	0.00341	11.72	<.0001
sleepqualitycat	1	0.00369	0.00173	2.13	0.0336

→ Path a details

Paths b and c':

Parameter Estimates						
Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	63.20629	3.39400	18.62	<.0001
CRPSI		1	126.59495	21.81671	5.80	<.0001
sleepqualitycat		1	1.99784	1.67034	1.20	0.2318

→ Path b details

→ Path c' details

Path c:

Parameter Estimates						
Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	68.26404	3.30762	20.64	<.0001
sleepqualitycat		1	2.46460	1.68236	1.46	0.1431

→ Path c details

Output From SAS Indirect Macro written by Hayes[143]

IV to Mediators (a paths)

bzxmat				
	Coeff	se	t	p
CRPSI	0.0037	0.0017	2.1258	0.0336

Direct Effects of Mediators on DV (b paths)

byzx2mat				
	Coeff	se	t	p
CRPSI	126.5949	21.8167	5.8027	0.0000

Total effect of IV on DV (c path)

byxmat				
	Coeff	se	t	p
SLEEPQUALITYCAT	2.4646	1.6824	1.4650	0.1431

Direct Effect of IV on DV (c' path)

cprimmat				
	Coeff	se	t	p
SLEEPQUALITYCAT	1.9978	1.6703	1.1961	0.2318

Indirect Effects of IV on DV through Mediators (ab paths)

spec				
	Effect	se	Z	p
TOTAL	0.4668	0.2338	1.9966	0.0459
CRPSI	0.4668	0.2338	1.9966	0.0459

****

BOOTSTRAP RESULTS FOR INDIRECT EFFECTS

Indirect Effects of IV on DV through Mediators (ab paths)

res				
	Data	Boot	Bias	SE
TOTAL	0.4668	0.4635	-0.0032	0.2206
CRPSI	0.4668	0.4635	-0.0032	0.2206

Bias Corrected and Accelerated Confidence Intervals

ci		
	Lower	Upper
TOTAL	-0.0006	0.8848
CRPSI	-0.0006	0.8848

Explanation for the Output

Note that the estimates for the paths are similar with both methods, and as described above, the products of ab = c-c'. The ab is the estimate of the indirect mediation effect, or the contribution of the mediatory variable to the relationship between and exposure and outcome. In this instance, the relationship between sleep quality and fasting insulin level (outcome) is explained by the mediatory variable (CRP) to a large extent (0.4668). That is, CRP contributes significantly (p=0.459) to the relationship between sleep quality and fasting insulin level.

Appendix G: Additional Related Manuscripts

Published

1. Kanagasabai T, Nie JX, Mason C, and Ardern CI. "Metabolic Syndrome and Any-Site, Prostate, Breast, and Colon Cancers in the U.S. Adult Population: NHANES 1999-2010." *Journal of Metabolic Syndrome*, 3(1) 2014: 135-142.

2. Kanagasabai T, Thakkar N, Churilla J, Kuk JL, and Ardern CI. Physical Activity Types in Metabolically Healthy Obese Adults: NHANES 1999-2006. *International Journal of Behavioral Nutrition and Physical Activity,* 12(1) 2015: 64.

Not published

1. Kanagasabai T, Dhanoa R, Kuk JL, and Ardern CI. Sleep and Metabolic Health in Adults with Obesity.

2. Chojnacki KC, Kanagasabai T, Riddell MC, and Ardern CI. Associations Between Sleep Quantity and Sleep Quality and Glycosylated Hemoglobin Levels in US Adults.

3. Kanagasabai T, K Alkhalaqi, Churilla J and Ardern CI. Normal weight is associated with optimal micronutrient levels, and micronutrient levels help predict metabolic syndrome.

4. Ardern CI, Kanagasabai T and Churilla J. American Diabetes Association Type 2 Diabetes Risk Test Sensitivity Analysis.

5. Chu J, Blajer B, Siswanto O, Kanagasabai T, Ardern CI and Balogh K. Effectiveness of a 7-week Community-based Diabetes Education Program.